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The Chemistry of 5-Oxodihydroisoxazoles. XII* Trapping of Derived Ketenimines with Lithium Amides and Alkyllithiums

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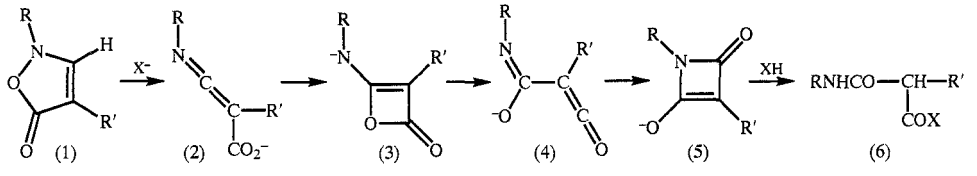
Abstract

Isoxazolones unsubstituted at C 3 react with lithium amides or alkyllithiums to give ketenimines. The presence of an ethoxycarbonyl group at C 4 allows capture of this species by addition of a second equivalent of the lithiated species to give enolates which can be alkylated *in situ*. The presence of a phenyl group at C 4 gives a ketenimine which reacts intramolecularly in the presence of lithium amides, whereas alkyllithiums undergo addition in synthetically useful processes.

Introduction

It is now generally accepted[1–3] that nucleophiles most frequently react with C 3 unsubstituted isoxazol-5-ones (1) by initially acting as bases and abstracting H 3 to form a ketenimine (2), which undergoes a number of transformations eventually leading to either the malonimide (5) or malonamide (6). We have recently reported reaction conditions[3] that allow the isolation of compounds derived from trapping of each of the intermediates between (1) and (6) (Scheme 1). During this study, an equivalent of alkyllithium or alkylamide was added slowly to the isoxazolone, allowing the rearrangement of (2) to (3)–(5) to be established. We now report on results when 2 equiv. of the alkyllithium or lithium amide are added rapidly, or inverse addition is used, and thereby form and react with the ketenimine (2) to generate enolates which can be alkylated *in situ*.



Scheme 1

* Part XI, *Aust. J. Chem.*, 1995, **48**, in press.

[1] Woodman, D. J., and Stonebraker, P. M., *Tetrahedron Lett.*, 1970, 4473.
[2] Woodman, D. J., Stonebraker, P. M., and Weiler, L., *J. Am. Chem. Soc.*, 1976, **98**, 6036.
[3] Prager, R. H., and Razzino, P., *Aust. J. Chem.*, 1994, **47**, 1673.

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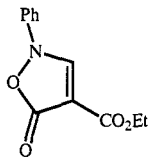
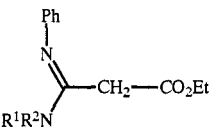
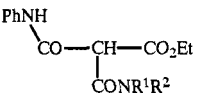


(7)



	R^1	R^2	
(8)	Pr^i	Pr^i	(9)
(10)	Et	Et	(14)
(11)	C_4H_8		(15)
(12)	C_5H_{10}		(16)
(13)	C_4H_8O		(17)



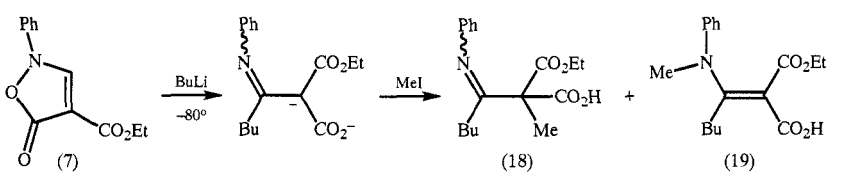
Results and Discussion

Addition of isoxazolone (7) to 2 equiv. of lithium diisopropylamide at −80° gave the addition compound (8) in 87% yield, with 13% of the malonamide (9), which might be expected by reaction of lithium diisopropylamide with the β-lactone (3) or the ketene (4). At −25° the respective ratio was 60 : 15, and above 0° only the malonamide (9) was found. Clearly the intramolecular rearrangement of (2) to (5) is accelerated as the temperature rises, relative to its rate of reaction with lithium diisopropylamide or isopropylamine. In addition, if hexamethylphosphoramide was added as cosolvent, the intramolecular rearrangements occurred even more rapidly: at −80° lithium diisopropylamide gave only 15% of (8) and 65% of (9). We have shown this reaction is general, obtaining products (10)–(17) in ratios that do not clearly represent any indication that steric factors or basicity are dominant (Table 1). Attempts to alkylate any anionic product *in situ* have not been successful (compare below).

Table 1. Products from reaction of (7) with lithium amides at −80°

Amide	Amide		Malonamide	
Lithium diisopropylamide	(8)	87%	(9)	13%
Lithium diethylamide	(10)	52%	(14)	47%
Lithium pyrrolidide	(11)	43%	(15)	57%
Lithium piperidide	(12)	45%	(16)	55%
Lithium morpholinide	(13)	82%	(17)	18%

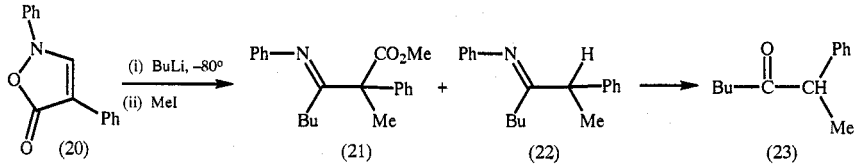
Rapid addition of 2 equiv. of alkyllithiums to the isoxazolone, followed by workup with methyl iodide, allowed the isolation of products obtained solely from addition of the alkyllithium to the ketenimine, followed by subsequent *C*- or *N*-methylation. Thus butyllithium and methyl iodide gave esters (18) and (19) in 24 and 38% yields respectively (Scheme 2).



Scheme 2

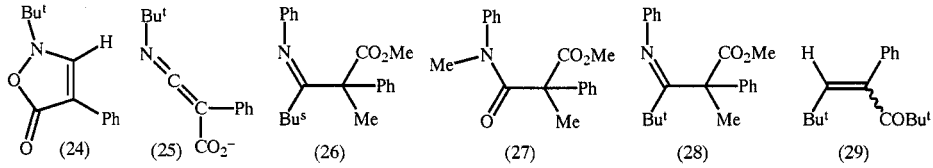
Since it appeared possible that the ethoxycarbonyl group at C 4 in (7) was affecting the acidity of H 3, the isoxazolone (20) was treated with 2 equiv. of butyllithium at −80°, followed by addition of methyl iodide. In this case the

major product isolated (78%) was the ester (21) in which *C*-methylation and carboxyl methylation had occurred. The minor product was the decarboxylated material (22), whose structure was confirmed by hydrolysis to the known ketone (23)[4] (Scheme 3).

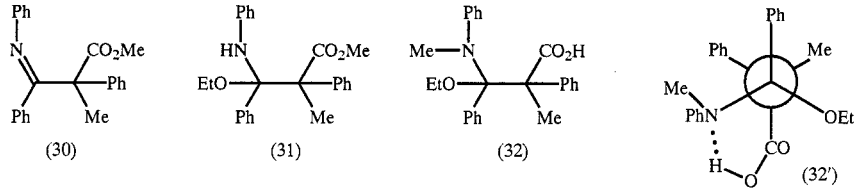


Scheme 3

The failure by Woodman to observe addition of alkyllithium to the isoxazolone (24) would now appear to be due to steric hindrance by the t-butyl group to addition to the ketenimine (25), which was isolated. The isoxazolone (20) gave similar reaction products when reacted with s-butyllithium, t-butyllithium, and phenyllithium.



The reactions tended to be extremely diagnostic about the quality of the alkyllithiums. Thus s-butyllithium, besides the major expected product (26) (82%), also gave 7% of the amido ester (27), indicative of traces of lithium hydroxide in the alkyllithium. The same by-product was obtained in the reaction of (20) with t-butyllithium. However, in this case besides the expected major product (28) (45%), small amounts of phenylhydroxylamine and the tetramethylphenylheptenone (29) were indicative of a second reaction pathway, presumably involving reaction at the lactone carbonyl group followed by addition/elimination at C 3.



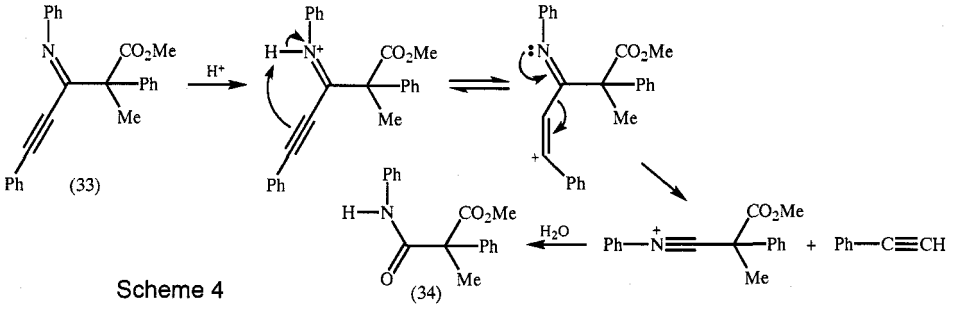
Phenyllithium, when freshly prepared, reacted with isoxazolone (20) in the ratio of 2 : 1 to give the expected ester (30) in 62% yield, but, when an older, commercial sample was used, this was replaced by the products of further addition of ethoxide* and partial *N*-methylation, namely (31) (15%) and (32)

* The ethoxy groups arise from lithium ethoxide, present in older samples of phenyllithium in ether.

[4] Nakada, M., Urano, Y., Kobayashi, S., and Ohno, M., *J. Am. Chem. Soc.*, 1988, **110**, 4826.

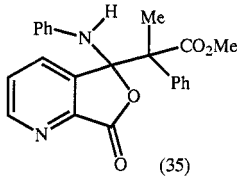
(67%) respectively. Both (31) and (32) were a mixture of diastereoisomers, and showed only very broad signals in the ^{1}H n.m.r. spectrum (300 MHz) at 20°. Raising the temperature to 58° sharpened all the signals, but the ^{13}C n.m.r. spectrum of (31) continued to show two ester carbonyl signals, and two ethyl groups, as expected. Clearly the considerable crowding about the central highly substituted carbon–carbon bond allows the slow exchange between a variety of conformers below 58°. In addition, the acid (32) underwent only extremely slow hydrogen/deuterium exchange, consistent with strong intramolecular hydrogen bonding, as in (32′) and other conformers.

When reacted with (20), lithium phenylacetylide gave two products: the expected imine (33) (53%) and the malonate amide (34) (24%). This amide was shown to be formed from (33) on workup, even when aqueous NH_4Cl was used at room temperature. A suggested pathway is shown in Scheme 4.



Scheme 4

N,*N*-Diisopropylpyridine-2-carboxamide was lithiated at C 3 with butyllithium,[5] and the product (2 equiv.) added to the isoxazol-5-one (20), followed by methyl iodide. Three products were isolated: the expected 'isobenzofuranones' (35) and (36), and the azetidinedione (37). The first two products clearly arise by addition of the amide carbonyl group to the first-formed imine, and the last by the intramolecular rearrangements detailed in Scheme 1.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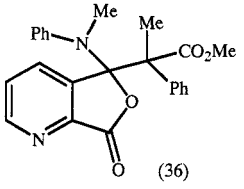
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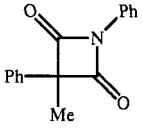
(37)

PhNHCOCH$_2$Ph

(38)

From the above comparison of the reactivity of (7) and (20) toward alkyllithium reagents, it appeared that the diphenylisoxazolone (20) formed a ketenimine with bases that was more prone to undergo internal rearrangements than that from (7). Hence it was not surprising to us to find that (20) failed to give amidines akin to (8) with lithium amides: in fact, a number of lithium amides all gave high yields of the azetidinedione (37) if the reaction was worked up with methyl iodide. Aqueous workup resulted in hydrolysis of the azetidinedione to the malonic acid amide, or decarboxylation to phenylacetamide (38).[3]

[5] Epsztajin, J., Berski, Z., Bresinski, J. Z., and Joswiak, A., *Tetrahedron Lett.*, 1980, **21**, 4739.

In conclusion, isoxazol-5-ones unsubstituted at C 3 react readily with 2 equiv. of alkyllithiums or aryllithiums to give products arising from addition at C 3 in synthetically useful yields, and the resulting ions may be alkylated *in situ* to give highly substituted products. The intermediate ketenimines can be trapped by lithium amides only if stabilized with an ester group.

Experimental

^{13}C and ^{1}H n.m.r. spectra were recorded at 75·50 and 300 MHz respectively. All spectra were recorded in $CDCl_3$, unless otherwise stated, which was used as a reference (77·04 ppm). Assignments of ^{13}C spectra with primes refer to phenylamino carbons; those with double primes refer to *C*-phenyl. All solvents were distilled and stored over drying agents under nitrogen. Centrifugal chromatography was performed by means of a Chromatotron (7924T) with silica gel 60 PF_{254}. It was found essential for all solvents involved in the radial chromatography to be purified to exclude traces of water, which led to poor resolution and decomposition of the products during the separation. General experimental details have been previously reported.[6]

Reaction of Isoxazol-5-one (7) with Lithium Diisopropylamide and Other Amides

A solution of freshly distilled diisopropylamine (0·25 g, 2·5 mmol) in tetrahydrofuran (50 ml) was cooled to −80° and butyllithium (1·79 ml, 2·5 mmol) added dropwise. The solution was allowed to warm to 0° for 15 min and cooled again to −80°. The mixture was stirred for 30 min and a solution of ethyl 5-oxo-2-phenyl-2,5-dihydroisoxazole-4-carboxylate (7) (300 mg, 1·2 mmol) in tetrahydrofuran (20 ml) was added over 5 min. The resultant light orange solution was stirred for 1 h and quenched with aqueous ammonium chloride. The products were separated by radial chromatography to afford ethyl 3-diisopropylamino-3-phenyliminopropanoate (8) (82%) and ethyl *N*,*N*-diisopropylcarbamoyl-*N*-phenylcarbamoylacetate (9) (13%). Each was characterized by direct comparison with an authentic sample.[7]

When hexamethylphosphoramide (2 ml, 11 mmol) was used, it was introduced into the reaction mixture 30 min after addition of isoxazol-5-one (7).

The various lithium amides used in similar reactions and the corresponding yields of products are collected in Table 1.

Ethyl 3-phenylimino-3-(pyrrolidin-1-yl)propanoate (11), not previously characterized, was isolated as a pale yellow viscous oil which decomposed on attempted distillation (90°/0·5 mm). Radial chromatography (t-butyl methyl ether/cyclohexane 1:5) gave a colourless *oil*, R_F 0·65 (Found: M^+, 260·3289. $C_{15}H_{20}N_2O_2$ requires M^+, 260·3294). ^{1}H n.m.r. δ 1·26, t, *J* 7·01 Hz, 3H; 1·87, m, 4H; 3·23, m, 4H; 3·88, s, 2H; 4·34, q, *J* 7·01 Hz, 2H; 6·90–7·41, m, 5H. ^{13}C n.m.r. δ 14·90, CH_3; 22·01, CH_2; 34·52, C 2; 46·15, CH_2N; 61·24, CH_2O; 119·68, C 4′; 123·01, C 2′; 128·32, C 3′; 154·78, C 1′; 167·90, C 1; 170·11, C 3. ν_{max} 3324, 1701, 1671, 1640, 1596 cm^{-1}. Mass spectrum *m/z* 260 (M), 231, 187.

Reaction of Isoxazol-5-one (7) with Butyllithium/Methyl Iodide

Isoxazol-5-one (7) (580 mg, 2·5 mmol) was dissolved in anhydrous tetrahydrofuran and cooled to −80° under nitrogen in the absence of light. Butyllithium (3·5 ml, 5 mmol) was added dropwise to the stirred reaction mixture over 5 min, with the resulting formation of a dark red colour. The solution was stirred for 1 h at −80°, then freshly distilled hexamethylphosphoramide (2 ml, 11 mmol) was added. After a further 1 h the reaction was quenched by addition of methyl iodide (0·45 ml, 4·3 mmol), and the mixture was stirred for 12 h. The solvent was removed under reduced pressure and cold saturated aqueous ammonium chloride (20 ml) was added, followed by extraction of the mixture with cold ethyl acetate.

[6] Singh, Y., and Prager, R. H., *Aust. J. Chem.*, 1992, **45**, 1811.
[7] Ang, K. H., Donati, C., Donkor, A., and Prager, R. H., *Aust. J. Chem.*, 1992, **45**, 2037.

The ethyl acetate fraction was further washed with cold saturated ammonium chloride (3×10 ml) to remove traces of hexamethylphosphoramide. The resultant organic fraction was dried and evaporated under reduced pressure to afford a red oil which was separated by radial chromatography on silica with dichloromethane/light petroleum (1:3) as the eluent to afford two components.

2-Ethoxycarbonyl-3-[methyl(phenyl)amino]hept-2-enoic acid (19) was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:3) as the eluent, to give a colourless oil (38%). The compound rapidly decomposed on standing, and had R_F values of 0·61 and 0·32 for the two systems respectively (Found: C, 67·0; H, 8·0; N, 4·5%; M^+, 305·1657. $C_{17}H_{23}NO_4$ requires C, 66·9; H, 7·6; N, 4·6%; M^+, 305·1627). ^{1}H n.m.r. δ 0·90, t, J 7·38 Hz, 3H; 1·24–1·34, m, 5H; 1·59, m, 2H; 2·58, m, 2H; 2·84, s, 3H; 4·20, q, J 7·38 Hz, 2H; 6·61–7·49, m, 6H, ArH, OH (D_2O exch.). ^{13}C n.m.r. δ 12·82, CH_3; 14·01, 14·11, CH_2; 22·22, CH_2; 25·66, CH_2; 41·09, NCH_3; 61·30, OCH_2; 112·48, C2; 117·23, C2′; 128·79, C4′; 129·77, C3′; 144·31, C1′; 151·31, C3; 163·41, C1; 167·91, CO. ν_{max} 3460, 3056, 2944, 1727, 1686 cm^{-1}. Mass spectrum m/z 305 (M), 260, 216, 160.

(E)- *and* (Z)-*2-Ethoxycarbonyl-2-methyl-3-phenyliminoheptanoic acids* (18) were eluted second, and the mixture was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:3) as the eluent, to give a yellow gum (24%), which had R_F values of 0·55 and 0·20 for the two systems respectively (Found: C, 66·9; H, 7·9; N, 4·5%; M^+, 305·1666. $C_{17}H_{23}NO_4$ requires C, 66·9, H, 7·9; N, 4·6%; M^+, 305·1627). ^{1}H n.m.r. δ 0·65, t, J 7·77 Hz, 3H; 1·22–1·47, m, 7H; 1·47, s, 3H; 2·25, m, 2H; 4·17, q, J 7·48 Hz, 2H; 6·66–7·39, m, 6H, ArH, OH (D_2O exch.). ^{13}C n.m.r. δ 12·77, CH_3; 13·34, CH_3; 14·14, CH_2; 25·64, CH_3; 29·27, CH_2; 30·57, CH_2; 52·39, 52·86, C2; 60·87, OCH_2; 118·64, C2′; 122·72, C4′; 128·85, C3′; 150·98, C3′; 171·43, CO_2H; 174·69, C1; 175·47, C3. ν_{max} 2944, 2866, 1733, 1655, 1588, 1461 cm^{-1}. Mass spectrum m/z 305 (M), 260, 216, 174, 160.

Reaction of 2,4-Diphenylisoxazol-5(2H)-one (20) with Alkyllithiums/Methyl Iodide

Typical procedure with butyllithium. Isoxazol-5-one (20) (0·4 g, 1·7 mmol) was dissolved in anhydrous tetrahydrofuran (100 ml), and cooled to −80° under nitrogen in the absence of light. Butyllithium (2·3 ml, 3·4 mmol, in hexane) was added dropwise over 1 min, with the resulting formation of a pale red colour. The solution was stirred for 30 min, and then freshly distilled hexamethylphosphoramide (2 ml, 11 mmol) was added. The reaction mixture was stirred for 1 h and was quenched by addition of methyl iodide (1 ml, 16 mmol), and allowed to warm up to room temperature for 12 h. The solvent was removed under reduced pressure and saturated aqueous ammonium chloride (20 ml) was added at 0°, followed by extraction of the mixture with cold ethyl acetate. The extracts were washed with cold saturated ammonium chloride (3×10 ml), dried and evaporated to afford a yellow oil which was separated by radial chromatography on silica with ether/light petroleum (1:3) as the eluent. *Methyl 2-methyl-2-phenyl-3-phenyliminoheptanoate* (21) was isolated as a dark red oil (78%) which decomposed on distillation (110°/0·1 mm). It was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:5) as the eluent, and was stored under dark anhydrous conditions to prevent decomposition (Found: C, 77·9; H, 7·8; N, 4·2%; M^+, 323·1877. $C_{21}H_{25}NO$ requires C, 77·9; H, 7·8; N, 4·3%; M^+, 323·1885). ^{1}H n.m.r. δ 0·55, t, J 6·55 Hz, 3H; 0·82–1·10, m, 4H; 1·98, s, 3H; 2·32, m, 2H; 3·79, s, 3H; 6·75–7·59, m, 10H. ^{13}C n.m.r. δ 13·19, C7; 22·94, CH_3; 22·87, C6; 29·31, C5; 31·43, C4; 52·37; 52·43, OCH_3; 61·51, C2; 118·73, C2′; 122·97, C4′; 127·39, C3′; 128·00, C4″; 128·30, C2″; 128·85, C3″; 140·34, C1′; 150·79, C1″; 174·24, C1; 174·69, C3. ν_{max} 1733, 1650, 1588 cm^{-1}. Mass spectrum m/z 323 (M), 203, 292, 264, 160.

The second fraction, isolated as a pale yellow oil (10%), consisted of (E)-*2-phenyl-3-phenyliminoheptane* (22) (Found: M^+, 265·1860. $C_{19}H_{23}N$ requires M^+, 265·1830). ν_{max} 1656 cm^{-1}. ^{1}H n.m.r. δ 0·72, t, J 7·00 Hz, 3H; 1·1–1·3, m, 4H; 1·40, d, J 7·00 Hz, 3H; 1·45, q, J 7·00 Hz, 1H; 3·73, q, J 7·00 Hz, 2H; 6·7–7·4, m, 10H. ^{13}C n.m.r. δ 13·89, CH_3; 17·47, CH_3; 22·71, CH_2; 29·26, CH_2; 32·17, CH_2; 47·56, CH; 119–129, CH; 140·79; 143·54; 176·28, C=N.

On acidic hydrolysis, or chromatography on silica, the imine (22) was converted into 2-phenylheptan-3-one (23) (Found: M^+, 190·1365. Calc. for $C_{13}H_{18}O$: M^+, 190·1357). ν_{max} 1713 cm^{-1}. Spectral data were consistent with those in the literature.[4]

Reaction of Isoxazol-5-one (20) with s-Butyllithium/Methyl Iodide

The crude reaction mixture was separated by radial chromatography on silica, with ether/light petroleum (1:5) as the eluent.

Methyl 2,4-dimethyl-2-phenyl-3-phenyliminohexanoate (26) was isolated as a pale yellow oil which decomposed on distillation (95°/0·05 mm) and was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:8) as the eluent (82%) (Found: C, 77·7; H, 7·7; N, 4·5%; M^+, 323·1881. $C_{21}H_{25}NO_2$ requires C, 77·9; H, 7·8; N, 4·3%; M^+, 323·1885). ^{1}H n.m.r. δ 0·55, t, J 6·55 Hz, 3H; 0·80–1·12, m, 5H; 1·99, s, 3H; 2·22, m, 1H; 3·84, s, 3H; 6·75–7·59, m, 10H. ^{13}C n.m.r. δ 13·21, C6; 22·55, CH_3; 23·15, CH_3; 28·32, C5; 32·01, C4; 53·88, OCH_3; 62·45, C2; 110·65, C2′; 122·56, C4′; 127·23, C3′; 128·34, C4″; 128·66, C2″; 128·98, C3″; 140·12, C1″; 151·01, C1′; 173·98, C1; 174·77, C3. ν_{max} 1746, 1665, 1589 cm^{-1}. Mass spectrum m/z 323 (M), 203, 292, 264, 160.

The minor product (*c.* 7%) was *methyl 2-[methyl(phenyl)carbamoyl]-2-phenylpropanoate* (27), isolated as a colourless oil (Found: M^+, 297·1386. $C_{18}H_{19}NO_3$ requires M^+, 297·1365). ν_{max} 1738, 1651, 1595, 1495 cm^{-1}. ^{1}H n.m.r. δ 1·75, s, 3H; 3·16, s, 3H; 3·72, s, 3H; 6·6–7·2, m, 10H. ^{13}C n.m.r. δ 27·59, CH_3; 52·40, OCH_3; 58·82, C2; 126·99; 127·19; 127·52; 127·55; 127·70; 128·13; 128·25; 128·91; 170·99; 172·29. NMe not detected. Mass spectrum m/z 297 (M, 9·8%), 205 (5), 163 (14), 134 (100), 84 (55).

Reaction of Isoxazolone (20) with t-Butyllithium/Methyl Iodide

The crude reaction mixture was separated by radial chromatography on silica, with ether/light petroleum (1:5). The least polar product was *2,2,6,6-tetramethyl-4-phenylhept-4-en-3-one* (29), isolated as a light yellow oil which rapidly decomposed on distillation (75°/0·05 mm) or on standing. It was purified by a second radial chromatography on silica, with dichloromethane/cyclohexane (1:3) as the eluent, to give a colourless oil (13%) (Found: M^+, 244·1845. $C_{17}H_{24}O$ requires M^+, 244·1827). ^{1}H n.m.r. δ 0·98, s, 9H; 1·37, s, 9H; 5·88, s, 1H; 7·26–7·28, m, 5H. ^{13}C n.m.r. δ 28·16, CH_3; 30·94, CH_3; 34·23, C2; 44·86, C6; 127·37, C4′; 127·67, C2′; 130·02, C3′; 130·42, C4; 136·64, C5; 142·97, C1′; 211·39, C3. ν_{max} 2958, 1682, 1471 cm^{-1}. Mass spectrum m/z 244 (M) 199, 171.

The second fraction was *N*-phenylhydroxylamine (10%), m.p. 80–83° (lit.[8] 81–82°), identified by direct comparison with an authentic sample.

The major fraction was *methyl 2,4,4-trimethyl-2-phenyl-3-phenyliminopentanoate* (28), isolated as a light yellow oil which decomposed on distillation (75°/0·05 mm). It was purified by a second radial chromatography on silica, with t-butyl methyl ether/cycloxhexane (1:8) as the eluent, to give a colourless oil (45%) which was stored under dark anhydrous conditions to prevent decomposition (Found: C, 77·8; H, 7·7; N, 4·3%; M^+, 323·1879. $C_{21}H_{25}NO_2$ requires C, 77·9; H, 7·8; N, 4·3%; M^+, 323·1885). ^{1}H n.m.r. δ 0·98, s, 9H; 1·85, s, 3H; 3·76, s, 3H; 6·70–7·70, m, 10H. ^{13}C n.m.r. δ 29·06, CH_3; 31·01, CH_3; 43·74, C4; 51·97; 52·00, OCH_3; 61·24, C2; 117·11, C2′; 121·02, C4′; 126·94, C3′; 127·46, C4″; 128·07, C2″; 128·31, C3″; 140·98, C1″; 150·74, C1′; 173·17, C1; 174·37, C3. ν_{max} 1738, 1661, 1591 cm^{-1}. Mass spectrum m/z 323 (M), 203, 292, 264, 160.

The most polar product (5%) was identified as methyl 2-[methyl(phenyl)carbamoyl]-2-phenylpropanoate (27), identical with the product characterized above.

Reaction of Isoxazolone (20) with Phenyllithium/Methyl Iodide

Freshly prepared phenyllithium (2 equiv.) in ether was added over 5 min in the usual way to the isoxazolone in tetrahydrofuran. Radial chromatography of the crude product gave only one pure product, *methyl 2-methyl-2,3-diphenyl-3-phenyliminopropanoate* (30), isolated as a colourless oil (62%) (Found: M^+, 343·1626. $C_{23}H_{21}NO_2$ requires M^+, 343·1572). ν_{max} 1732, 1651, 1593 cm^{-1}. ^{1}H n.m.r. δ 1·83, s, 3H; 3·70, s, 3H; 6·6–7·5, m, 15H. Mass spectrum m/z 343 (M, 15%), 284 (6), 197 (22), 180 (100), 71 (90).

Use of a commercial sample, which clearly contained considerable lithium ethoxide, gave two products separable by radial chromatography with t-butyl methyl ether/cyclohexane (1:9).

[8] 'Dictionary of Organic Compounds' 5th Edn, Vol. 5 (Chapman & Hall: London 1982).

Methyl 3-ethoxy-2-methyl-2,3-diphenyl-3-phenylaminopropanoate (31) was isolated as a pale red oil which decomposed on distillation (110°/0·05 mm). It decomposed on standing and was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:3) as the eluent, to give a colourless oil (15%) (Found: C, 76·7; H, 6·9; N, 3·2. $C_{25}H_{27}NO_3$ requires C, 77·0; H, 6·9; N, 3·5%). ^{1}H n.m.r. δ 1·28, t, J 7·34 Hz, 3H; 1·79, s, 3H; 3·55, s, 3H; 4·23, q, J 7·34 Hz, 2H; 6·55–7·65, m, 15H; 7·81, br s, 1H, NH (D_2O exch.). ^{1}H n.m.r. δ 14·16, CH_3; 24·13, CH_3; 52·42, OCH_2; 58·03, C 2; 62·94, OCH_3; 73·94, C 3; 115·39; 120·40; 120·63; 122·25; 127·23; 127·31; 127·47; 127·54; 128·03; 140·13; 141·29; 146·33; 170·94; 171·83, C 1. ν_{max} 3150, 1721, 1643, 1598 cm^{-1}. Mass spectrum m/z 311 (M − 78), 253, 197.

3-Ethoxy-2-methyl-3-[methyl(phenyl)amino]-2,3-diphenylpropanoic acid (32) was isolated as a pale red oil which decomposed on distillation (110°/0·05 mm) and was purified by further radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:9) as the eluent, as a colourless oil (67%) (Found: C, 76·8; H, 7·4; N, 3·4%; $M^+ - 1$, 388·1915. $C_{25}H_{27}NO_3$ requires C, 77·1; H, 6·9; N, 3·6%. $C_{25}H_{26}NO_3$ requires 388·1913). ^{1}H n.m.r. δ 1·35, t, J 7·12 Hz, 3H; 1·79, s, 3H; 3·15, s, 3H; 4·20, q, J 7·12 Hz, 2H; 6·70–7·65, m, 15H; 7·91, br s, 1H, D_2O exch. ^{13}C n.m.r. δ 13·94, CH_3; 27·69, CH_3; 39·86, NCH_3; 58·98, C 2; 61·27, OCH_2; 73·45, C 3; 126·62; 126·91; 127·22; 127·35; 127·50; 128·19; 128·54; 128·75; 128·86; 140·40; 143·54; 170·94; 171·83, C 1. ν_{max} 3303, 3150, 1720, 1655, 1588, 1488 cm^{-1}. Mass spectrum m/z 388 (M − 1), 373, 329, 237.

Reaction of Isoxazol-5-one (20) with Lithium Phenylacetylide/Methyl Iodide

Butyllithium (1·7 ml, 2·4 mmol, in hexane) was slowly added to freshly distilled phenylacetylene (0·25 g, 2·4 mmol) in tetrahydrofuran (100 ml) at −80° under nitrogen. The mixture was stirred for 30 min and a solution of isoxazol-5-one (20) (300 mg, 1·2 mmol) in tetrahydrofuran (5 ml) was added. The resultant dark red solution was stirred for 30 min and hexamethylphosphoramide (2 ml, 11 mmol) was added. After 1 h, the reaction was worked up as above. Radial chromatography on silica, with ethyl acetate/light petroleum (1:5) as the eluent, afforded two compounds.

Methyl 2-methyl-2,5-diphenyl-3-phenyliminopent-4-ynoate (33) was isolated as a pale green oil which decomposed on distillation (110°/0·05 mm) or on standing, and was purified by further radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:9) as the eluent, to give a colourless oil (63%) (Found: C, 81·7; H, 6·0; N, 3·7%; M^+, 367·1564. $C_{25}H_{21}NO_2$ requires C, 81·7; H, 5·8; N, 3·8%; M^+, 367·1572). ^{1}H n.m.r. δ 2·11, s, 3H; 3·83, s, 3H; 7·02–7·58, m, 15H. ^{13}C n.m.r. δ 22·96, CH_3; 52·71, OCH_3; 60·55, C 2; 83·10, C 5; 98·28, C 4; 120·68, C 2′; 122·12, C 2″; 124·97, C 4′; 125·36, C 3″; 127·50, C 3′; 128·02, C 4‴; 128·18, C 4″; 128·34, C 2″; 128·48, C 3″; 139·99, C 1″; 145·14, C 1‴; 150·96, C 1′; 155·68, C 3; 173·47, C 1. ν_{max} 3120, 2201, 1727, 1584 cm^{-1}. Mass spectrum m/z 367 (M), 366, 260, 204.

Methyl 2-phenyl-2-phenylcarbamoylpropanoate (34) decomposed on distillation (110°/0·05 mm) and was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:5) as the eluent, as a colourless oil (29%) (Found: C, 71·9; H, 6·2; N, 4·6%; M^+, 283·1217. $C_{17}H_{17}NO_3$ requires C, 72·1; H, 6·0; N, 4·9%; M^+, 283·1208). ^{1}H n.m.r. δ 1·91, s, 3H; 3·85, s, 3H; 7·09–7·58, m, 10H; 8·62, br s, 1H, NH (D_2O exch.). ^{13}C n.m.r. δ 23·04, C 3; 53·22, OCH_3; 60·16, C 2; 119·95, C 2; 124·53, C 4; 126·67, C 4″; 128·05, C 3″; 128·99, C 2″; 129·09, C 3′; 137·73, C 1′; 140·48, C 1″; 168·51, CO; 174·22, C 1. ν_{max} 1737, 1712, 1678, 1594 cm^{-1}. Mass spectrum m/z 283 (M), 224, 164, 132.

Hydrolysis of Methyl 2-Methyl-2,5-diphenyl-3-phenyliminopent-4-ynoate (33)

The acetylene (33) (100 mg, 0·3 mmol) in dioxan (50 ml) was stirred with saturated ammonium chloride (10 ml) for 1 h. Extraction with ethyl acetate gave a brown oil which was separated by radial chromatography on silica to give methyl 2-phenyl-2-phenylcarbamoylpropanoate (34) (60%) and phenylacetylene (30%).

Reaction of Isoxazol-5-one (20) with 2-Diisopropylcarbamoyl-3-lithiopyridine/Methyl Iodide

Butyllithium (1·7 ml, 2·4 mmol, in hexane) was slowly added over 15 min to freshly recrystallized *N*,*N*-diisopropylpyridine-2-carboxamide (490 mg, 2·4 mmol) in ether (100 ml)

at −80° under nitrogen. After 1 h a solution of isoxazol-5-one (20) (300 mg, 1·2 mmol) in tetrahydrofuran (30 ml) was added. The resultant red solution was stirred for 30 min and freshly distilled hexamethylphosphoramide (2 ml, 11 mmol) was added. After 1 h, the reaction mixture was treated with methyl iodide, and worked up as above. Radial chromatrography on silica afforded three products.

The first product was identified as 3-methyl-1,3-diphenylazetidine-2,4-dione (37) (23%), m.p. 46–48°, identical to the sample characterized below.

Methyl 2-(5-[methyl(phenyl)amino]-7-oxo-5,7-dihydrofuro[3,4-b]pyridin-5-yl)-2-phenylpropanoate (36) was isolated as a yellow gum which was subsequently purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:2) as the eluent (yield 27%) (Found: C, 71·5; H, 5·9; N, 6·9. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%). ^{1}H n.m.r. (40°) δ 1·75, s, 3H; 3·20, s, 3H; 3·72, s, 3H; 6·57–8·35, br m, 13H. ^{13}C n.m.r. δ 27·59, CH_3; 40·06; 40·14, NCH_3; 52·37, OCH_3; 58·82, C2; 103·39, C3; 118·13; 126·99; 127·35; 127·83; 128·14; 128·73; 128·79; 128·92; 141·32; 145·14; 147·11; 151·23; 155·92; 171·03; C1; 172·32. ν_{max} 3112, 1732, 1653, 1589 cm^{-1}. Mass spectrum *m/z* 297 (M − 105), 238, 163, 134.

Methyl 2-(7-oxo-5-phenylamino-5,7-dihydrofuro[3,4-b]pyridin-5-yl)-2-phenylpropanoate (35) was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:1) as the eluent, to yield a yellow solid (31%), m.p. >300° (Found: C, 71·2; H, 5·4; N, 6·9. $C_{23}H_{20}N_2O_4$ requires C, 71·1; H, 5·2; N, 7·2%). ^{1}H n.m.r. (40°) δ 1·91, s, 3H; 3·84, s, 3H; 7·04–8·65, br m, 13H; 8·79, br s, 1H, NH (D_2O exch.). ^{13}C n.m.r. (40°) δ 23·04, CH_3; 53·25, OCH_3; 60·16, C2; 103·21, C3; 119·95; 121·79; 124·53; 126·67; 127·03; 128·81; 129·08; 132·39; 136·91; 137·44, 140·48; 147·51; 148·94; 168·52; C1; 174·20, CO. ν_{max} 3325, 3122, 1737, 1712, 1678, 1678, 1594 cm^{-1}. Mass spectrum *m/z* 266 (M − 122), 164, 132, 103.

Reaction of 2,5-Diphenylisoxazol-5(2H)-one (20) with Lithium Amides/Methyl Iodide

Typical procedure. A solution of freshly distilled diisopropylamine (0·25 g, 2·5 mmol) in tetrahydrofuran (100 ml) was cooled to −80° and butyllithium (1·79 ml, 2·5 mmol) added. The solution was allowed to warm to 0° for 15 min and cooled again to −80°. A solution of isoxazol-5-one (20) (300 mg, 1·2 mmol) in tetrahydrofuran (15 ml) was slowly added over 10 min; the resultant pale orange solution was stirred for 30 min, and then freshly distilled hexamethylphosphoramide (2 ml, 11 mmol) added. After 1 h methyl iodide (1·8 g, 12·5 mmol) was added and the reaction was worked up as above. The crude compound was separated by radial chromatography on silica. *3-Methyl-1,3-diphenylazetidine-2,4-dione* (37) was purified by a second radial chromatography on silica, with t-butyl methyl ether/cyclohexane (1:5) as the eluent. The oil solidified on standing, and was recrystallized from ether as white needles (86%), m.p. 46–48° (Found: C, 76·2; H, 5·4; N, 5·5%; M^+, 251·0952. $C_{16}H_{13}NO$ requires C, 76·4; H, 5·2; N, 5·5%; M^+, 251·0946). ^{1}H n.m.r. δ 1·91, s, 3H; 7·21–7·98, m, 10H. ^{13}C n.m.r. δ 20·17, CH_3; 68·57, C3; 119·29, C2′; 125·57, C4′; 126·99, C4″; 128·41, C3″; 129·02, C2″; 129·16, C3′; 134·29, C1′; 135·50, C1″; 170·57, C2, C4. ν_{max} 3112, 1854, 1741m 1599, 1491 cm^{-1}. Mass spectrum *m/z* 251 (M), 180, 132, 119.

If the reaction was quenched with aqueous ammonium chloride instead of methyl iodide, phenyl(*N*-phenylcarbamoyl)acetic acid[9] was obtained in nearly quantitative yield.

The use of lithium diethylamide, lithium 2,2,6,6-tetramethylpiperidide, lithium butylamide or lithium t-butylamide gave essentially identical results.

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[9] Redmon, B. C., U.S. Pat. 2,782,231 (*Chem. Abstr.*, 1957, **51**, 1057d).