A New Acylative Cycloaddition Reaction

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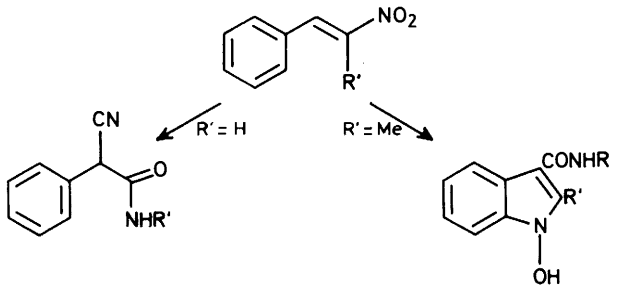
A new procedure for the intramolecular nitrile oxide cycloaddition reaction (INOC) is described. The procedure involves the generation of a nitrile oxide by the addition of isocyanide to an α,β-unsaturated nitroalkene.

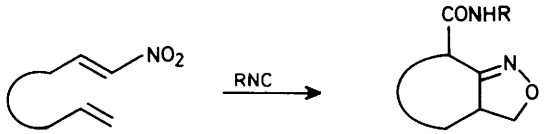
Nitrile oxides were known before the turn of the century,[1a] but their instability precluded their synthetic utility for many years. In 1927 cycloaddition reactions of nitrile oxides were demonstrated,[1b] but Huisgen[1c] later demonstrated the *in situ* generation of nitrile oxides, leading to the exploitation of their full potential.[1d]

In this paper we report our full experimental results on a new method for generating nitrile oxides, by way of a conjugate addition to nitroalkenes.[2] Foucaud *et al.*[3] published an elegant synthesis of *N*-hydroxyindoles, which relied on the addition of isocyanides to β-nitrostyrenes (Scheme 1).



Scheme 1.

The mechanism for the above transformation should proceed along similar lines to that reported earlier by Saegusa *et al.*[4] If only one equivalent of isocyanide was used we wondered if the intermediary nitrile oxide could be trapped with a dipolarophile prior to its deoxygenation (Scheme 2).



Scheme 2.

In order to study the reaction a stable, readily available nitroalkene was required. We therefore chose to prepare 1-(*o*-allylphenyl)-2-nitroethene (**5**) as shown in Scheme 3.

o-Allylbromobenzene (**2**) was prepared in 65% yield by a copper(I)-catalysed coupling reaction.[5] The product was formylated by treating the Grignard reagent derived from compound (**2**) with *N*,*N*-dimethylformamide (DMF) to yield aldehyde (**3**), which was then converted into the nitroalkene (**5**) in 68% yield.

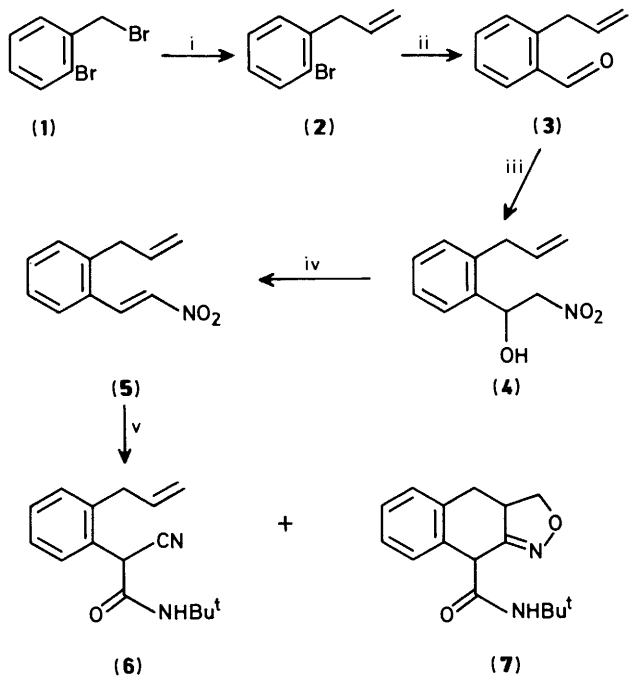
Initially, a solution of the nitroalkene (**5**) in benzene was treated with phenyl isocyanide at 80 °C. No reaction was observed, and we thus selected a more nucleophilic isocyanide to promote the desired reaction. The next experiment was conducted in [$^2H_6$]benzene with t-butyl isocyanide, resulting in the formation of the cyano amide (**6**). This result gave us great encouragement and the reaction was repeated using acetonitrile as solvent. At an initial 0.5M concentration of nitroalkene we observed formation of the desired tricyclic amide (**7**) in 48% yield (Table).

The tricyclic amide (**7**) was shown to be a 2:1 mixture of diastereoisomers by high-field ^1H n.m.r. spectroscopy. The

Table.

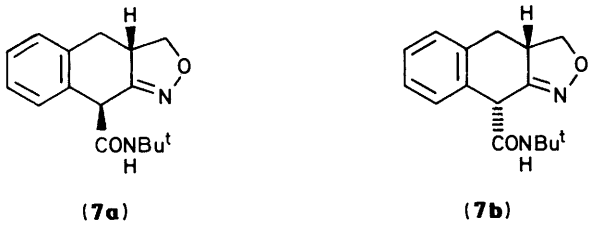
Entry	Solvent	[(5)]/M	Temp./°C (time)	Yield (%) (5)	(6)	(7)
1	MeCN	0.95	80 (26 h)	11		22
2	MeCN	0.95	80 (21 h)	27	7	38
3	MeCN	0.5	80 (20 h)	38[a]	10[a]	34
4	MeCN	0.5	80 (66 h)	34	17	48
5	MeCN	0.3	80 (4 days)			26
6	MeCN	0.5	60 (5.5 days)	33[a]	26[a]	10[a]
7	Dioxane	0.95	80 (29 h)	20[a]	40[a]	40[b]
8	Dioxane	0.3	80 (4 days)	36[a]	36[a]	20
9	Dioxane	0.5	100 (45 h)[c]			

[a] Based on proton n.m.r. analysis of the mixture. [b] Crude yield. [c] Some (**5**) was present (t.l.c.) but conditions were apparently too harsh.



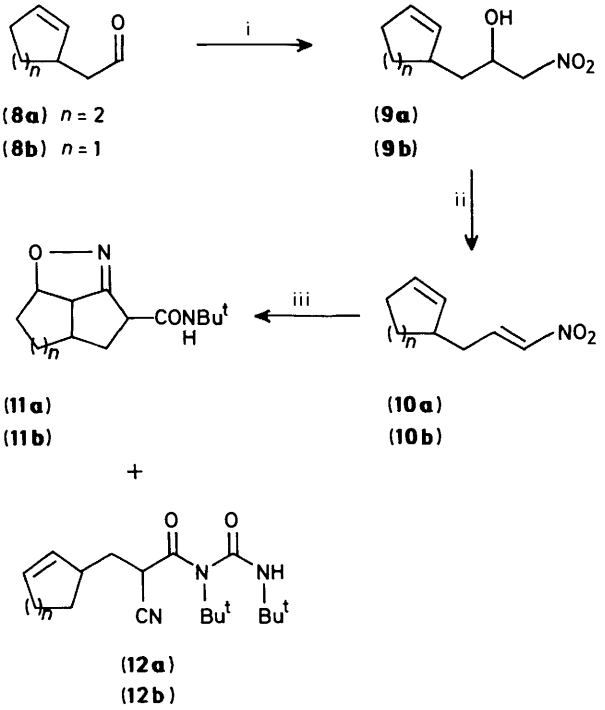
Scheme 3. *Reagents and conditions:* i, CH_2=CHBr, Mg, CuI, 2,2′-bipyridyl, THF, PhH; ii, Mg, DMF, THF, 0 °C; iii, $MeNO_2$, KOH–MeOH, pH 8: then H_2SO_4, pH 4; iv, MsCl, Et_3N, CH_2Cl_2; v, Bu^{t}NC, MeCN, 80 °C

relative stereochemistries of the two diastereoisomers were tentatively assigned since the *syn* relationship between the amide and the methine hydrogen in (**7a**) results in the signal for the latter being further downfield than in (**7b**). Hence compound (**7a**) is assigned as the major diastereoisomer.



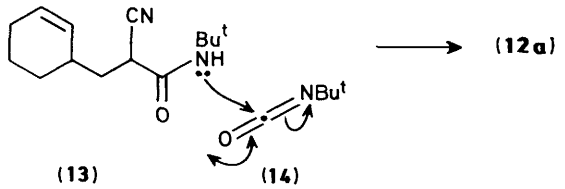
(**7a**) (**7b**)

Further studies were carried out to attempt to establish the generality of this new reaction. Having used a terminal alkene we decided to investigate the use of a cyclic alkene as the dipolarophile. Thus, the nitroalkenes (**10**) were prepared according to Scheme 4.



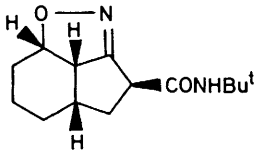
Scheme 4. *Reagents and conditions:* i, $MeNO_2$, KOH–MeOH, pH 8; then H_2SO_4, pH 4; ii, MsCl, Et_3N, CH_2Cl_2; iii, Bu^{t}NC, MeCN, 80 °C

At a 0.5M concentration of nitroalkene (**10a**) in acetonitrile we obtained the desired tricyclic dihydroisoxazole (**11a**) in 64% yield. This was accompanied by a 28% isolated yield of the acylurea (**12a**) which presumably arose from the reaction of the initially formed cyano amide (**13**) and isocyanate (**14**) that was generated during the formation of (**13**) (Scheme 5).

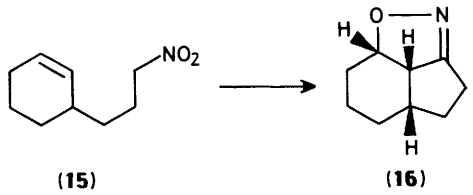


Scheme 5.

When a 0.3M solution of the nitroalkene (**10a**) in acetonitrile was treated with t-butylisocyanide (1.2 mol equiv.) and stirred for 4 days at 80 °C the tricyclic amide (**11a**) was isolated in 88% yield. A detailed examination of the high-field ^1H n.m.r. spectrum of (**11a**) showed that four diastereoisomers were present (1:1:1:1). One of these isomers was separated by flash chromatography; the other three appeared as a single spot on t.l.c. The single separated diastereoisomer was shown by n.O.e. n.m.r. studies to have the following relative stereochemistry.

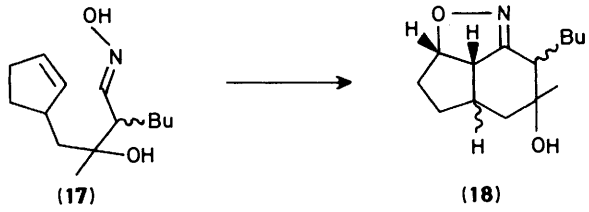


It was interesting to note that Curran and Jacobs[6] have synthesized a similar tricyclic molecule using a standard INOC procedure (Scheme 6).



Scheme 6.

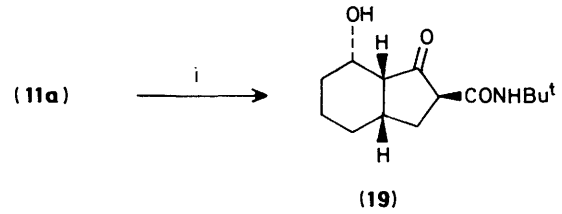
They did not comment on the stereochemistry of the product but in an earlier preparation Wollenberg [7] claimed the 'all *cis*' stereochemistry. Both groups reported the reductive cleavage of compound (**16**) to the β-hydroxy ketone (**17**) which was again said to be 'all *cis*.' Another compound bearing a resemblance to our dihydroisoxazole (**11a**) was also reported[7] as shown in Scheme 7.



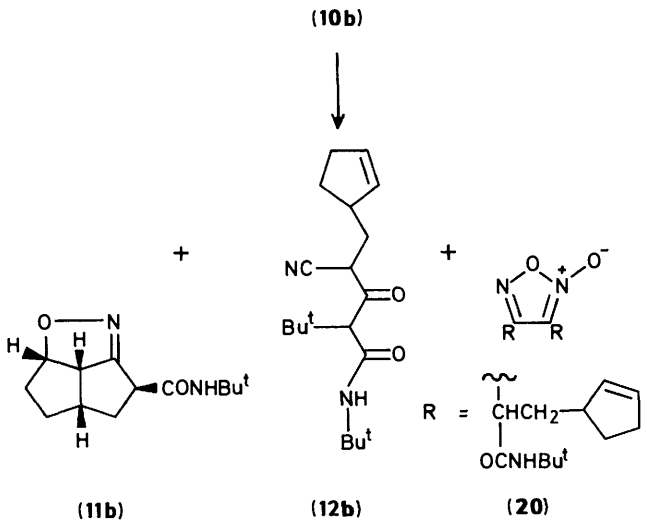
Scheme 7.

The INOC reaction of oxime (**17**) gave a mixture of four diastereoisomers of the cycloadduct (**18**). It is possible that in this case—as in ours—the situation of a group α to the nitrile oxide has a marked effect on the diastereofacial selectivity of the INOC reaction with an alkene. When the diastereoisomeric mixture (**11a**) was treated with hydrogen/palladium on charcoal in aqueous ethanol–acetic acid solution, a single diastereoisomer was obtained. By comparison with the aforementioned literature[6,7] the product was assigned as the β-hydroxy ketone (**19**) (Scheme 8), the single isomer arising presumably from a retroaldol/aldol sequence.[8]

Having established that the reaction with a cyclic alkene would proceed well, we investigated a second example. The cyclopentenyl nitroalkene (**10b**) was made as shown in Scheme 4. Reaction of a 0.3M solution of this nitroalkene in acetonitrile with t-butyl isocyanide as before gave three products (Scheme 9). The isolation of the furoxan (**20**) supported the mechanistic



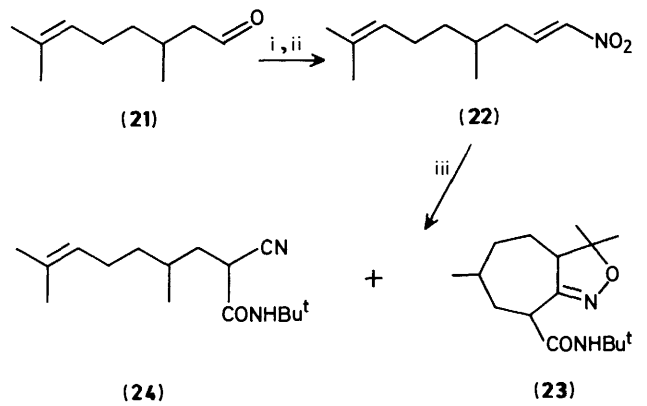
Scheme 8. *Reagents:* i, H_2/Pd–C, aqueous ethanol–acetic acid



Scheme 9.

pathway involving a nitrile oxide, since these readily dimerize to furoxans.

The isolation of a single diastereoisomer (**11b**) was encouraging, although the low (36%) yield was slightly disappointing. We therefore turned our attention to the acyclic trisubstituted alkene (**22**), prepared from citronellal (**21**) in 88% yield (Scheme 10). Reaction of the nitroalkene (**22**) under the



Scheme 10. *Reagents and conditions:* i, $MeNO_2$, KOH–MeOH, pH 8; then H_2SO_4, pH 4; ii, MsCl, Et_3N, CH_2Cl_2; iii, Bu^{t}NC, MeCN, 80 °C

previously described conditions gave only the cyano amide (**24**) and recovered starting material (**22**).

Reducing the concentration of (**22**) to 0.05M in acetonitrile gave the cyano amide (**24**) in 52% yield with little of the desired product (**23**). Reaction of an excess (3 mol equiv.) of the nitroalkene (**22**) with t-butyl isocyanide (1 mol equiv.) in acetonitrile led to the isolation of compound (**23**) in 40% yield (based on isocyanide). The bicyclic dihydro isoxazole (**23**) was found to be a 1:1 mixture of diastereoisomers as judged by the t-butyl signals in the high-field proton n.m.r. spectrum. All other signals were overlapping, preventing any prediction of relative stereochemistry.

Experimental

General.—Where appropriate, solvents were dried prior to use in the following manner; tetrahydrofuran (THF) was distilled from sodium and benzophenone, and acetonitrile, benzene, and toluene were all distilled from calcium hydride immediately prior to use. Light petroleum refers to the fraction boiling in the range 40—60 °C. Suction flash chromatography was conducted using Merck Kieselgel 60H (Art 7736) whilst flash chromatography used silica gel 60 (230—400 mesh). I.r. spectra were taken on a Perkin-Elmer 298 spectrometer.[1] ^{1}H N.m.r. spectra were run at 60 MHz on a Perkin-Elmer R24B, at 100 MHz on a Varian Associates XL100, at 400 MHz on a Bruker machine (care of Beecham Pharmaceuticals), and at 360 MHz on a Bruker AM360 with tetramethysilane as internal standard in deuteriochloroform. The ^{13}C n.m.r. spectra were run on a Bruker AM360 machine at 100.61 MHz in deuteriochloroform with $SiMe_4$. Mass spectra were recorded on a Kratos MS30 spectrometer with a DS 55S data system.

o-*Allylbromobenzene* (**2**).—A freshly prepared THF solution of vinylmagnesium bromide (0.125 mol) was stirred for 30 min, then benzene (25 ml) was added. A mixture of *o*-bromobenzyl bromide (**1**) (10 ml, 0.08 mol), copper(I) iodide (1.52 g, 0.008 mol), and 2,2′-bipyridyl (1.25 g, 0.008 mol) was prepared under nitrogen in a 500 ml flask and cooled to 0 °C. The vinylmagnesium bromide solution was transferred by cannula as rapidly as possible to the stirred dibromide (1) mixture. This caused immediate darkening and the reaction mixture reached reflux. (**CAUTION**: on one occasion a violent exothermic reaction was observed. This was probably due to inefficient mixing.) The reaction mixture was allowed to settle to room temperature during 2 h, then was stirred for a further 3 h. Solid ammonium chloride was added followed by ether (100 ml) and water (100 ml). The mixture was transferred to a beaker and conc. aqueous ammonia (3 ml) was added. After the mixture had been stirred for 1.5 h the organic phase was separated and the deep blue aqueous phase was extracted with ether (4 × 100 ml). The combined mother liquor and extracts were washed successively with dil. hydrochloric acid and saturated aqueous sodium hydrogen carbonate and dried ($MgSO_4$). Concentration under reduced pressure followed by distillation under reduced pressure afforded the known bromide (**2**)[5] (10.24 g, 65%), b.p. 52—54 °C at 0.2 mmHg; $\nu_{max.}$(CCl_4) 1 640 cm^{-1}; δ_H(60 MHz) 7.60—6.94 (4 H, m, ArH), 6.18—5.74 (1 H, m, CH_2CH=CH_2), 5.15 (1 H, s, br, *cis* CH=C*H*H), 5.01 (1 H, d, *J* 7 Hz, *trans* CH=CH*H*), and 3.50 (2 H, d, *J* 7 Hz, CH_2CH=CH_2); *m/z* 198 (30%), 196 (30), and 117 (100).

o-*Allylbenzaldehyde* (**3**).[9]—A solution of *o*-allylbromobenzene (**2**) (10.23 g, 0.05 mol) in THF (50 ml) was added to magnesium turnings (1.32 g, 1.1 mmol equiv.) in THF (50 ml) under nitrogen at such a rate as to maintain reflux. (The reaction was initiated by the addition of a crystal of iodine and warming.) The reaction was stirred for 30 min at room temperature before being cooled to 0 °C. A mixture of freshly distilled DMF (3.9 ml, 0.05 mol) and THF (30 ml) was added to the stirred mixture during 5 min. (No temperature rise or sticky precipitate was observed as had been indicated in the literature.[10]) The mixture was stirred in the ice–bath for 45 min then at room temperature for 4 h before being cautiously added to a water (150 ml)–ether (100 ml) mixture. The organic layer

was separated and the aqueous phase was made acidic with conc. hydrochloric acid before being further extracted with ether (3 × 150 ml). The combined organic phases were washed successively with saturated aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml) and dried ($MgSO_4$). Concentration under reduced pressure afforded a pale brown oil, which was distilled under reduced pressure to give *o*-allylbenzaldehyde (**3**) (6.18 g, 85%) (Found: M^+, 146.0737. Calc. for $C_{10}H_{10}O$: *M*, 146.0732); $\nu_{max.}$(film) 1 690s, 1 640w, 1 600m, and 1 570w cm^{-1}; δ_H(60 MHz) 3.7—3.9 (2 H, m, $ArCH_2$), 4.7—6.5 (3 H, m, $CH{=}CH_2$), 7.2—8.0 (4 H, m, ArH), and 10.25 (1 H, s, O=CH); *m/z* 146 (M^+, 29%), 145 (27), 131 (100), 91 (59), and 77 (28); $\lambda_{max.}$(EtOH) 290, 250, and 210 nm (ε 1 715, 10 990, and 12 060 dm^3 mol^{-1} cm^{-1}).

1-(o-*Allylphenyl*)-2-*nitroethanol* (**4**).—A mixture of the aldehyde (**3**) (1.02 g, 7 mmol) and freshly distilled nitromethane (3.79 ml, 70 mmol) was stirred under nitrogen and treated with 3M methanolic potassium hydroxide until pH 8 was attained. This gave rise to a 7 °C temperature rise (to 29 °C). After being stirred for 1 h the solution was acidified to pH 4 with conc. sulphuric acid. The mixture was added to water (30 ml) and extracted with ether (2 × 10 ml). The extracts were combined, washed successively with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml), and dried ($MgSO_4$). Concentration under reduced pressure followed by column chromatography over silica with dichloromethane as eluant yielded the *nitro alcohol* (**4**) (1.04 g, 71%), b.p. 112 °C at 0.25 mmHg (Kugelrohr) (Found: C, 63.7; H, 6.5; N, 6.4%; $C_{11}H_{13}NO_3$ requires C, 63.7; H, 6.3; N, 6.8%); $\nu_{max.}$(film) 3 540m, 3 450m sh, 1 640m, 1 565s, and 1 380m cm^{-1}; δ_H(60 MHz) 7.1—7.8 (4 H, m, ArH), 4.8—6.4 (4 H, m, $ArCHOH$ and $CH{=}CH_2$), 4.3—4.7 (2 H, m, CH_2NO_2), 3.4—3.7 (2 H, m, $CH_2C{=}$), and 2.75 (1 H, br s, D_2O exch. OH); *m/z* 207 (M^+, 0.2%), 146 (50), 131 (100), and 91 (68); $\lambda_{max.}$(EtOH) 215 nm (6 300 dm^3 mol^{-1} cm^{-1}).

(E)-o-*Allyl*-β-*nitrostyrene* (**5**).—The nitro alcohol (**3**) (3.7 mmol, 0.76 g) and mesyl chloride (0.32 ml, 1.1 mol equiv.) were stirred under nitrogen in dichloromethane (10 ml). Triethylamine (1.03 ml, 2 mol equiv.) was added during 5 min, and the reaction mixture boiled gently. The mixture was stirred at room temperature for 1.75 h during which time a precipitate formed. The reaction mixture was added to water (20 ml), the organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 10 ml). The combined extracts were washed successively with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by suction flash chromatography with dichloromethane as eluant furnished the *nitrostyrene* (**5**) (0.67 g, 96%); b.p. 70—80 °C at 0.1 mmHg (Kugelrohr) (Found: C, 70.2; H, 5.95; N, 7.5. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%); $\nu_{max.}$(film) 1 635s, 1 600s, 1 515s, and 1 340s cm^{-1}; δ_H(60 MHz) 8.2 (1 H, d, *J* 14.0 Hz, $CH{=}CHNO_2$), 7.1—7.7 (5 H, m, ArH and $=CHNO_2$), 4.7—5.8 (3 H, m, $CH{=}CH_2$), and 3.4—3.7 (2 H, m, $ArCH_2$); $\lambda_{max.}$(EtOH) 310, 227, and 215 nm (10 700, 6 300, and 6 900 dm^3 mol^{-1} cm^{-1}).

2-(o-*Allylphenyl*)-2-*cyano*-N-*t*-*butylacetamide* (**6**) *and* N-*t*-*Butyl*-5-*oxa*-4,11-*azatricyclo*[7.4.0.0^{3,7}]*trideca*-3,9,11,12-*tetraene*-2-*carboxamide* (**7**).—t-Butyl isocyanide (0.14 ml, 1.2 mol equiv.) was added to a mixture of the nitrostyrene (**5**) (190 mg, 1 mmol) and acetonitrile (2 ml). The solution was stirred at 80 °C under nitrogen for 66 h and then allowed to cool to room temperature. Light petroleum (5 ml) was added followed by sufficient ether to permit the light petroleum and acetonitrile to mix. The supernatant was decanted and the resultant solid was washed with light petroleum to leave the essentially pure tricyclic dihydroisoxazole (**7**) as a white solid (82 mg, 30%). The supernatant and washings were combined and concentrated under reduced pressure and the residue was washed with light petroleum to afford a further crop (48 mg, 18%) of the *tricyclic dihydroisoxazole* (**7**); R_F (CH_2Cl_2) 0.6; m.p. (from ethyl acetate) 206—207 °C (decomp.) (Found: C, 70.4; H, 7.5; N, 10.25%; M^+ + 1, 273.1599. $C_{16}H_{20}N_2O_2$ requires C, 70.55; H, 7.4; N, 10.3%; *M* + 1, 273.1603); $\nu_{max.}$(CH_2Cl_2) 3 440w and 1 690s cm^{-1}; $\nu_{max.}$(Nujol) 3 280m, 3 080w, 1 695s, and 1 560m cm^{-1}; δ_H(360 MHz) a 2:1 mixture of diastereoisomers was present giving signals at δ 7.1—7.4 (4 H, m, ArH), 5.86 and 6.11 (1 H, 2br s, NH), 4.62 and 4.66 (1 H, 2 dd, *J* 8.0 and 10.4 Hz and 8.1 and 9.9 Hz, respectively, H_aH_bCO), 4.54 (1 H, s, $ArCHC{=}O$), 4.11 and 4.08 (1 H, apparent t, *J* 8.0 Hz and dd, *J* 8.2 and 11.1 Hz, respectively, H_aH_bCO), 3.8—3.9 and 3.4—3.6 (1 H, 2 m, $ArCH_2CHCH_2$), 3.31 and 3.09 (1 H, 2 dd, *J* 7.5 and 15.9 Hz and 6.0 and 14.Hz, respectively, $ArCH_aH_b$), 2.86 and 2.9—3.05 (1 H, dd, *J* 11.1 and 15.9 Hz and m respectively, $ArCH_aH_b$), and 1.35 and 1.34 (9 H, 2 s, Bu^t); *m/z* (CI, NH_3) 273 (M^+ − BuNCO, 100%), 116 (29), and 57 (19); $\lambda_{max.}$(EtOH) 273, 265, and 215 nm (290, 310, and 10 230 dm^3 mol^{-1} cm^{-1}).

The light petroleum washings were combined and concentrated under reduced pressure to furnish a sticky beige residue (120 mg). This was shown by 60 MHz ^1H n.m.r. to be a 2:1 mixture of the cyano amide (**6**) (34% based upon available isocyanide) and starting material (**5**) (17%). A sample of the *cyano amide* (**6**) was obtained pure for characterization, R_F (CH_2Cl_2) 0.25; m.p. (from dichloromethane–light petroleum) 114—115 °C (Found: M^+, 256.1553. $C_{16}H_{20}N_2O$ requires *M*, 256.1576); $\nu_{max.}$(CH_2Cl_2) 3 400w and 1 690s cm^{-1}; $\nu_{max.}$(Nujol) 3 300m, 2 240vw, and 1 670s cm^{-1}; δ_H(60 MHz) 7.2—7.5 (4 H, m, ArH), 4.8—6.3 (4 H, m, NH and $CH{=}CH_2$), 4.7 (1 H, s, $ArCHCN$), 3.42 (2 H, br d, *J* 6 Hz, $ArCH_2$), and 1.25 (9 H, s, Bu^t); *m/z* 256 (M^+, 0.4%), 157 (36), 130 (40), 116 (73), and 57 (100); $\lambda_{max.}$(EtOH) 270, 265, 260, and 215 nm (535, 610, 625, and 6 170 dm^3 mol^{-1} cm^{-1}).

1-(*Cyclohex*-2-*enyl*)-3-*nitropropan*-2-*ol* (**9a**).—The aldehyde (**8a**)[11] (2.0 g, 0.016 mol) was treated with nitromethane as in the preparation of nitro alcohol (**4**). Purification by flash chromatography with ether–light petroleum (1:1) as eluant yielded the *nitro alcohol* (**9a**) (2.43 g, 82%); b.p. 90—100 °C at 0.7 mmHg (Kugelrohr) (Found: C, 58.6; H, 8.4; N, 7.4%; M^+ + 1, 186.1124. $C_9H_{15}NO_3$ requires C, 58.35; H, 8.2; N, 7.6%; *M* + 1, 186.1130); $\nu_{max.}$(film) 3 400m, 2 940s, 1 555s, and 1 385m cm^{-1}; δ_H(360 MHz) two diastereoisomers were present in a 1:1 ratio, giving signals at δ 5.7—5.8 (1 H, m, $=CHCH_2$), 5.52 and 5.63 (1 H, 2 br dd, each *J* 2.3 and 10.3 Hz, $=CHCH$), 4.34—4.49 (3 H, m, $HOCHCH_2NO_2$), 2.92 and 2.93 (1 H, 2 d, each *J* 5.8 Hz, slow D_2O exch., OH), 2.23—2.38 (1 H, m, $CH_2CHC{=}$), and 1.23—2.03 (8 H, m, $CH_2CH_2CH_2CHCH_2$); *m/z* (CI, NH_3) 186 (M^+ + 1, 4%), 185 (M^+, 0.2), 168 (MH^+ − H_2O, 5), 125 (MH^+ − CH_2NO_2, 45), 95 (72), 81 (100), 79 (35), and 67 (41).

(E)-3-(3-*Nitroallyl*)*cyclohexene* (**10a**).—The nitro alcohol (**9a**) (0.94 g, 5.1 mmol) was dehydrated using the procedure for the preparation of the nitrostyrene (**5**). Purification by flash chromatography over silica with 30% ether–light petroleum gave the *nitroalkene* (**10a**) (0.7 g, 82%); b.p. 85—90 °C at 0.7 mmHg (Kugelrohr) (Found: C, 64.8; H, 7.9; N, 8.3%; M^+, 167.0963. $C_9H_{13}NO_2$ requires C, 64.6; H, 7.8; N, 8.4%; *M*, 167.0946); $\nu_{max.}$(film) 3 110w, 3 020m, 2 940s, 2 860s, 1 525s, and 1 350s cm^{-1}; δ_H(360 MHz) 7.2—7.3 (1 H, m, $HC{=}CHNO_2$), 7.01 (1 H, dd, *J* 1.7 and 13.3 Hz, $HCNO_2$), 5.74—5.79 (1 H, m, $CH_2CH_2CH{=}$), 5.52 (1 H, dd, *J* 2.2 and 10.1 Hz, $=CHCH$), 2.2—2.4 (3 H, m, $=CCHCH_2C{=}$), and 1.23—2.03 (6 H, m, $CH_2CH_2CH_2$); *m/z* 167 (M^+, 0.3%), 81 (100), 79 (14), and 77 (6); $\lambda_{max.}$(EtOH) 234 nm (10 280 dm^3 mol^{-1} cm^{-1}).

N-[2-*Cyano*-3-(*cyclohex*-2-*enyl*)*propionyl*]-N,N′-*di*-t-*butylurea* (**12a**) *and* N-t-*Butyl*-2-*oxa*-3-*azatricyclo*[5.3.1.0^{4,11}]*undec*-3-*ene*-5-*carboxamide* (**11a**).—t-Butyl isocyanide (0.19 ml, 1.2 mol equiv.) was added to a 0.5M solution of the nitroalkene (**10a**) (250 mg, 1.5 mmol) in acetonitrile (5 ml). The reaction mixture was stirred at 80 °C under nitrogen for 3 days. The reaction mixture was cooled, concentrated under reduced pressure, and the residue was purified by flash chromatography over silica with ether as eluant to furnish the *acylurea* (**12a**) (70 mg, 28% based upon available isocyanide), R_F (ether–light petroleum, 1:1) 0.55; m.p. (from light petroleum)156—158 °C (Found: M^+, 333.2423. $C_{19}H_{31}N_3O_2$ requires M, 333.2416); $\nu_{max.}(CH_2Cl_2)$ 3 400w, 2 970m, 2 940m, 1 680s, 1 610s, and 1 530s cm^{-1}; δ_H(360 MHz) 6.56 (1 H, s, NH), 5.65—5.7 (1 H, m, =*H*CCH$_2$), 5.54—5.6 (1 H, m, =C*H*CH), 4.13 (1 H, s, CHCN), 2.3—2.55 (3 H, m, =HCC*H*C*H*$_2$CHCN), 1.9—2.1 (2 H, m, CH$_2$C=), and 1.1—1.8 (22 H, m, C*H*$_2$C*H*$_2$CH and 2 Bu^t); *m*/*z* 333 (M^+, 2%), 234 (M^+ − BuNCO, 1), 177 (4), 153 (11), 81 (7), and 57 (100); $\lambda_{max.}$(EtOH) 316 nm (4 000 dm^3 mol^{-1} cm^{-1}).

Further elution of the column provided the tricyclic *dihydroisoxazole* (**11a**) (240 mg, 64%); R_F (ether–light petroleum 1:1) 0.1 (Found: C, 67.1; H, 8.9; N, 11.2%; M^+, 250.1684. $C_{14}H_{22}N_2O_2$ requires C, 67.15; H, 8.9; N, 11.2%; M, 250.1681); $\nu_{max.}(CH_2Cl_2)$ 3 400w, 2 980m, 2 950m, 1 680s, and 1 520s cm^{-1}. This product was chromatographed again with ether as eluant to give a single diastereoisomer (see text for the discussion of relative stereochemistry) as the first fraction, R_F (ether) 0.37; m.p. (from ether–light petroleum) 132—133 °C; δ_H(400 MHz) 6.03 (1 H, br s, NH), 4.76 (1 H, overlapping dt, *J* 5.5 and 9.2 Hz, 1-H), 3.74 (1 H, apparent br t, *J* 8.7 Hz, 11-H), 3.50 (1 H, apparent dt, *J* 2.2 and 8.9 Hz, 5-H), 2.79 (1 H, ddd, *J* 6.8, 9.1, and 13.8 Hz, 6-H), 2.25—2.35 (2 H, m, 7- and 6-H), 1.95—2.1 (1 H, m, 10-H), 1.75—1.85 (1 H, m, 8-H), 1.5—1.6 (1 H, m, 9-H), 1.33 (9 H, s, Bu^t), 1.15—1.35 (1 H, m, 9-H), and 0.8—1.05 (2 H, m, 8- and 10-H); δ_C(100.61 MHz) 171.30 (C=O), 167.71 (C-4), 79.66 (C-1), 56.49 (C-5), 51.68 (*C*Me$_3$), 40.14 (C-6), 40.07 (C-11), 33.13 (C-7), 28.70 (C*Me*$_3$), and 28.89, 28.40, and 20.64 (C-8, -9, and -10); $\lambda_{max.}$(EtOH) 320 and 270 nm (520 and 2 590 dm^3 mol^{-1} cm^{-1}).

The second fraction from the column was found to contain a further three diastereoisomers (plus a trace of the above diastereoisomer); R_F (ether) 0.31; δ_H(360 MHz) 6.05 and 7.05 (1 H, 2 br, NH), 4.7—4.8 (1 H, m, 1-H), 3.65—3.8 (1 H, m, 11-H), 3.45—3.55 (1 H, m, 5-H), 2.55—2.85 (2 H, m, 6-H$_2$), 2.2—2.35 (1 H, m, 7-H), 1.95—2.1 (1 H, m, 10-H), 1.7—1.85 (1 H, m, 8-H), 1.5—1.6 (1 H, m, 9-H), 1.34, 1.36, and 1.37 (9 H, s, Bu^t), 1.1—1.35 (1 H, m, 9-H), and 0.75—1.0 (2 H, m, 8- and 10-H); *m*/*z* 250 (M^+, 8%), 235 (M^+ − 15, 2), 150 (M^+ − BuNCOH$^+$, 100), 134 (27), 132 (14), 91 (12), and 57 (34).

The preparation of the tricyclic dihydroisoxazole (**11a**) was repeated at 0.3M concentration of the nitroalkene in acetonitrile. The reaction was stopped after 4 days and after work-up afforded (**11a**) in 88% yield. This product was identical (n.m.r. and t.l.c.) with that already described.

2-*Hydroxy*-9-*oxo*-N-t-*butylbicyclo*[4.3.0]*nonane*-8-*carboxamide* (**19**).—The four-component diastereoisomeric dihydroisoxazole (**11a**) (250 mg, 1 mmol) was mixed with 5% palladium–charcoal (50 mg), ethanol (10 ml), water (1 ml), and acetic acid (2 ml). The reaction mixture was stirred under hydrogen (balloon) for 1.5 h, then filtered and added to saturated aqueous sodium hydrogen carbonate (40 ml). The aqueous mixture was extracted with ethyl acetate (4 × 20 ml) and the combined extracts were washed successively with saturated aqueous sodium hydrogen carbonate (20 ml) then brine (20 ml), and dried (Na_2SO_4). Concentration under reduced pressure afforded essentially pure hydroxy ketone (**19**) as a white solid. This was purified by flash chromatography over silica with ethyl acetate as eluant to afford the pure *hydroxy ketone* (**19**) (215 mg, 85%); m.p. (from ethyl acetate–light petroleum) 128—130 °C (Found: C, 66.6; H, 9.1; N, 5.6%; M^+, 253.1647. $C_{14}H_{23}NO_3$ requires C, 66.4; H, 9.2; N, 5.5%; M, 253.1678); $\nu_{max.}(CH_2Cl_2)$ 3 580w, 3 460w, 3 390w, 2 950m, 2 870m, 1 730s, and 1 680s cm^{-1}; δ_H(360 MHz) 6.37 (1 H, br s, NH), 3.65—3.83 (1 H, m, 2-H), 3.26 (1 H, s, D_2O exch., OH), 2.7—3.15 (1 H, m, 1-H), 2.28—2.36 (1 H, m, 8-H), 1.55—2.2 (6 H, m, 3-, 4-, 5-, 6-H, and 7-H$_2$), and 1.05—1.55 (12 H, m, 3-, 4-, 5-H, and Bu^t. The t-butyl showed as a singlet at 1.35); *m*/*z* 253 (M^+, 6.7%), 235 (M^+ − H_2O, 5), 179 (11), 136 (20), 72 (27), 58 (100), and 57 (33).

1-(*Cyclopent*-2-*enyl*)-3-*nitropropan*-2-*ol* (**9b**).—The aldehyde (**8b**)[11] (0.72 g, 8.5 mmol) was treated with nitromethane as in the preparation of nitro alcohol (**4**). Purification by flash chromatography over silica with ether–light petroleum (1:1) as eluant yielded the *nitro alcohol* (**9b**) (0.7 g, 48%); b.p. 90—100 °C at 1.0 mmHg (Kugelrohr) (Found: MH^+ − H_2O, 154.0959. $C_8H_{13}NO_3$ requires MH^+ − H_2O, 154.0868); $\nu_{max.}$(film) 3 440m, 3 060w, 2 950m, 2 860m, 1 615vw, 1 555s, and 1 380s cm^{-1}; δ_H(100 MHz) 5.6—5.9 (2 H, m, olefinic protons), 4.3—4.6 (3 H, m, HOC*H*C*H*$_2$NO$_2$), 2.88 (1 H, br s, =CC*H*CH$_2$), 2.5—2.64 (1 H, m, D_2O exch., OH), 1.9—2.5 (3 H, m, =CC*H*$_2$-CH$_a$*H*$_b$CH), and 1.2—1.9 (3 H, m, *H*$_a$H$_b$CCHC*H*$_2$CHOH); *m*/*z* no M^+ observed; 154 (MH^+ − 18, 0.14%), 109 (16), 81 (45), 80 (40), 79 (41), and 67 (100).

(E)-3-(3-*Nitroallyl*)*cyclopentene* (**10b**).—The nitro alcohol (**9b**) (338 mg, 1.98 mmol) was dehydrated using the procedure for the preparation of the nitrostyrene (**5**). The reaction mixture was stirred for just 20 min after the addition of the triethylamine. Purification by flash chromatography over silica with 30% ether–light petroleum as eluant furnished the *nitroalkene* (**10b**) (215 mg, 71%) as a pale yellow oil, b.p. 80—85 °C at 0.8 mmHg (Kugelrohr) (Found: C, 62.4; H, 7.4; N, 8.85. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.2%); $\nu_{max.}$(film) 3 120w, 3 060w, 2 950w, 2 860m, 1 650m, 1 530s, and 1 355s cm^{-1}; δ_H(100 MHz) 7.34 (1 H, dt, *J* 7.5 and 14.0 Hz, *H*C=CHNO$_2$), 6.98 (1 H, br d, *J* 14.0 Hz, =CHNO$_2$), 5.74—5.9 (1 H, m, CH$_2$C*H*=CHCH), 5.44—5.74 (1 H, m, CH$_2$CH=C*H*), 2.7—3.1 (1 H, m, CH$_2$C*H*CH$_2$), 1.9—2.6 (5 H, m, =CC*H*$_2$CH$_a$*H*$_b$-CHC*H*$_2$), and 1.2—1.7 (1 H, m, CH$_2$*H*$_a$H$_b$CCHCH$_2$); *m*/*z* no M^+ observed due to a fragmentation giving 67 (cyclopentenyl$^{+\bullet}$, 100%; $\lambda_{max.}$(EtOH) 230 nm (8 810 dm^3 mol^{-1} cm^{-1}).

N-[2-*Cyano*-3-(*cyclopent*-2-*enyl*)*propionyl*]-N,N′-*di*-t-*butylurea* (**12b**), 3,4-*Bis*-[2-(*cyclopent*-2-*enyl*)-1-t-*butylcarbamoylethyl*]*furazan* N-*Oxide* (**20**), *and* N-t-*Butyl*-2-*oxa*-3-*azatricyclo*[5.2.1.0^{4,10}]*dec*-3-*ene*-5-*carboxamide* (**11b**).—A 0.3M solution of the nitroalkene (**10b**) (335 mg, 2.17 mmol) in acetonitrile (7.25 ml) was treated with t-butyl isocyanide (0.27 mol, 1.2 mol equiv.). The solution was stirred under nitrogen at 80 °C for 2.5 days and then cooled. Concentration under reduced pressure followed by flash chromatography over silica with ether–light petroleum (1:1) as eluant gave the *acylurea* (**12b**) as the first fraction (36 mg, 10%); R_F (ether–light petroleum 1:1) 0.46; m.p. (from light petroleum) 148—149 °C (Found: M^+, 319.2251. $C_{18}H_{29}N_3O_2$ requires M, 319.2260); $\nu_{max.}(CH_2Cl_2)$ 3 400m, 3 050w, 2 970m, 1 670s, 1 540m, and 1 490s cm^{-1}; δ_H(360 MHz) 6.55 (1 H, s, NH), 5.75 (1 H, apparent dq, *J* 2.1 and 5.7 Hz, =CH), 5.64 (1 H, apparent dq, *J* 2.1 and 5.7 Hz, =CH), 4.13 (1 H, br s, O=CC*H*CN), 2.9—3.05 (1 H, m, =CC*H*CH$_2$), 2.65 (1 H, dd, *J* 6.6 and 14.2 Hz, CHCH$_a$*H*$_b$CHCN), 2.2—2.45 (2 H, m, C*H*$_2$C=), 2.27 (1 H, dd, *J* 8.4 and 14.2 Hz, CHC*H*$_a$H$_b$CHCN), 1.95—2.1 (1 H, m, CH$_2$CH$_a$*H*$_b$CH), 1.4—1.5 (1 H, m, CH$_2$C*H*$_a$H$_b$CH), and 1.38 and 1.43 (18 H, 2 s, 2 × Bu^t); *m*/*z* 319 (M^+, 4%), 220 (M^+ − BuNCO, 2), 163 (8), 153 (11), 97 (24), 67 (19), and 57 (100).

Further elution of the column furnished the *furoxan* (**20**) as the second fraction (61 mg, 12%); R_F (ether–light petroleum 1:1) 0.24; m.p. (from light petroleum) 35—36 °C (Found: C, 66.5; H, 8.45; N, 11.7. $C_{26}H_{40}N_4O_4$ requires C, 66.1; H, 8.5; N, 11.9%); $\nu_{max.}(CH_2Cl_2)$ 3 430m, 2 970m, 1 695s, and 1 520s cm^{-1}; δ_H(360 MHz) 5.99 (2 H, 2 × br s, NH), 5.8—5.84 (2 H, apparent pair of overlapping dqs, *J* 2 and 5.7 Hz, 2 × =CH), 5.64—5.69 (2 H, apparent pair of overlapping dqs, *J* 2 and 5.7 Hz, 2 × CH), 3.30 (2 H, dd, *J* 5.5 and 9.3 Hz, 2 × O=CCH), 2.8—2.91 (2 H, m, 2 × CC*H*CH_2), 2.33—2.39 (4 H, m, 2 × CH_2C=), 1.88—2.18 (6 H, m, 2 × $CHCH_2CH_2CH_aH_bCH_2$), 1.4—1.49 (2 H, m, 2 × $CH_2CH_aH_bCH$), and 1.34 (18 H, s, 2 × Bu^t).

Continued elution of the chromatography column furnished the *tricyclic dihydroisoxazole* (**11b**) (185 mg, 36%), R_F (ether–light petroleum 1:1) 0.07; m.p. (from ether–light petroleum) 115—116 °C (Found: M^+, 236.1546. $C_{13}H_{20}N_2O_2$ requires *M*, 236.1525); $\nu_{max.}(CH_2Cl_2)$ 3 430m, 2 980m, 1 675s, 1 625w, and 1 515s cm^{-1}; δ_H(360 MHz) the dihydroisoxazole (**11b**) was a single diastereoisomer (see text) giving signals at δ 5.05 (1 H, br, s, NH), 4.99 (1 H, dd, *J* 6.0 and 7.6 Hz, 1-H), 4.14 (1 H, dd, *J* 7.6 and 7.9 Hz, 10-H), 3.42 (1 H, dd, *J* 4.7 and 8.6 Hz, 5-H), 2.80 (1 H, ddd, *J* 4.6, 7.6, and 13.8 Hz, 6-H), 2.56 (1 H, apparent quintet, *J* 8.6 Hz, 7-H), 2.13 (1 H, dd, *J* 8.6 and 13.8 Hz, 6-H), 2.05 (1 H, dd, *J* 6.6 and 14.4 Hz, 9-H), 1.89 (1 H, dt, *J* 6.5 and 12.6 Hz, 8-H), 1.6—1.7 (1 H, m, 9- or 8-H), 1.2—1.35 (1 H, m, 8- or 9-H), and 1.35 (9 H s, Bu^t); *m/z* 236 (M^+, 5%), 138 (13), 137 (M^+ – BuNCO, 100), 120 (48), 109 (23), 67 (13), and 57 (91).

(E)-4,8-*Dimethyl*-1-*nitronona*-1,7-*diene* (**22**).—Citronellal (**21**) (9.1 ml, 0.05 mol) was treated with nitromethane as in the preparation of nitro alcohol (**4**). The resultant nitro alcohol was not purified but was dehydrated with mesyl chloride as in the preparation of compound (**5**). Purification by suction flash chromatography over silica with ether–light petroleum mixtures as eluant (0—30% ether; 15% polarity gradient) afforded the *nitroalkene* (**22**) (8.68 g, 88%). A sample was distilled (Kugelrohr), but larger scale distillation led to decomposition; b.p. 90—95 °C at 0.2 mmHg (Kugelrohr) (Found: C, 67.1; H, 9.9; N, 6.85. $C_{11}H_{19}NO_2$ requires C, 67.0; H, 9.7; N, 7.1%); $\nu_{max.}$(film) 3 110w, 2 920s, 1 650s, 1 525s, and 1 350s cm^{-1}; δ_H(360 MHz) 7.26 (1 H, dt, *J* 7.9 and 13.3 Hz, 2-H), 6.98 (1 H, dd, *J* 1.5 and 13.2 Hz, 1-H), 5.08 (1 H, dt, *J* 1.5 and 7.0 Hz, 7-H), 2.24—2.31 (1 H, m, 3-H), 1.96—2.15 (3 H, m, 3-H and 6-H_2), 1.64—1.74 (1 H, m, 4-H), 1.61 and 1.69 (6 H, 2 s, 8-Me and 9-H_3), 1.15—1.45 (2 H, m, 5-H_2), and 0.95 (3 H, d, *J* 6.4 Hz, 4-Me); *m/z* no M^+ observed but fragment ions included; 111 (M^+ – 86, 4%), 109 (20), 95 (15), 86 (1), 81 (17), 69 (100), and 55 (55); $\lambda_{max.}$(EtOH) 240 nm (10 830 dm^3 mol^{-1} cm^{-1}).

2-*Cyano*-4,8-*dimethyl*-N-*t*-*butylnon*-7-*enamide* (**24**) *and* N-*t*-*Butyl*-4,10,10-*trimethyl*-9-*oxa*-8-*azabicyclo*[5.3.0]*dec*-7-*ene*-6-*carboxamide* (**23**).—A solution of the nitroalkene (**22**) (0.9 g, 4.5 mmol), t-butyl isocyanide (0.16 ml, 1.5 mmol), and acetonitrile (9 ml) was stirred at 80 °C under nitrogen for 3.25 h. The reaction mixture was then cooled, concentrated under reduced pressure, and purified by suction flash chromatography over silica with ethyl acetate–light petroleum mixtures as eluant (0—100% ethyl acetate; 10% polarity gradient). Unchanged starting material (**22**) (650 mg) was first recovered. Further elution then yielded the *cyano amide* (**24**) (140 mg, 60% based upon available isocyanide); R_F (ethyl acetate–light petroleum 1:1) 0.64; b.p. 125—130 °C at 0.05 mmHg (Kugelrohr) (Found: M^+, 264.2258. $C_{16}H_{28}N_2O$ requires *M*, 264.2202); $\nu_{max.}$(film) 3 215m, 3 080w, 2 980m, 2 940m, 2 260w, 1 700sh, and 1 665s cm^{-1}; δ_H(100 MHz) 6.96 (1 H, br s, NH), 5.08 (1 H, br t, *J* 7 Hz, 7-H), 3.2—3.4 (1 H, m, 2-H), and 0.8—2.2 (25 H, m, 3-H_2, 4-H, 4-Me, 5-H_2, 6-H_2, 8-Me, 9-H_3, and Bu^t); *m/z* 264 (M^+, 4.8%), 208 (M^+ – Bu, 2), 97 (23), and 57 (100).

Further elution of the chromatography column furnished the bicyclic dihydroisoxazole (**23**) (170 mg, 40% based upon available isocyanide); R_F (ethyl acetate–light petroleum 1:1) 0.1; m.p. (from ether–light petroleum) 86—87 °C; $\nu_{max.}(CH_2Cl_2)$ 2 960m, 2 940m, and 1 620s cm^{-1}; δ_H(360 MHz) the product was found to be a 1:1 mixture of diastereoisomers with the ratio being unchanged by recrystallization, and giving signals at δ 0.91 (6 H, 2 s, 10-Me_2); 1.20—1.55 (15 H, m, 2-H, 3-H, 4-Me, 5-H, and Bu^t; the Bu^t resonated as two singlets at δ 1.36 and 1.4), 6.33 and 6.38 (1 H, 2 s, NH), 3.0 (1 H, br s, 6-H), and 1.65—1.95 (5 H, m, 1-, 2-, 3-, 4-, and 5-H); *m/z* no M^+ was observed under either EI or CI conditions. However, the CI mass spectrum contained the fragments 182 (M^+ – BuNCO, 100%) and 167 (M^+ – BuNCO – Me, 97) which were wholly consistent with the dihydroisoxazole structure (**23**). The EI mass spectrum was dominated by fragments resulting from an apparent initial cycloreversion to the nitroalkene (**22**). The fragments compared favourably with those in the mass spectrum of the pure nitroalkene (**22**) and included *m/z* 109 (30%), 95 (35), 81 (52), 69 (45), and 55 (57).

Note: The nitroalkene (**22**) did not show any fragmentation to give a peak with *m/z* 182, therefore its assignment as a primary fragment ion from compound (**23**) is not unreasonable.

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References

1 (*a*) Ch. Grundmann and P. Grunager, 'The Nitrile Oxides, Versatile Tools of Theoretical and Preparative Chemistry,' Springer Verlag, New York, 1971; (*b*) C. Weygand and E. Bauer, *Justus Liebigs Ann. Chem.*, 1927, **459**, 123; (*c*) R. Huisgen, *Proc. Chem. Soc.*, 1961, 357; (*d*) A. P. Kozicowski, *Acc. Chem. Res.*, 1984, **17**, 410.
2 J. Knight and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1987, 189.
3 A. Foucaud, C. Razorilakana-Rabearivony, E. Loukakou, and H. Person, *J. Org. Chem.*, 1983, **48**, 3639.
4 T. Saegusa, S. Kobayashi, Y. Ito, and S. Marino, *Tetrahedron*, 1972, **28**, 3389.
5 M. Chandler and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1984, 322.
6 D. P. Curran and P. B. Jacobs, *Tetrahedron Lett.*, 1985, **26**, 2031.
7 R. H. Wollenberg and J. E. Goldstein, *Synthesis*, 1980, 757.
8 J. Knight, Ph.D. Thesis, University of Southampton, 1986.
9 J. A. Kampmeier, S. H. Harris, and I. Mergelsberg, *J. Org. Chem.*, 1984, **49**, 621.
10 G. A. Ohlah, G. K. Surya-Prakash, and M. Arvanaghi, *Synthesis*, 1984, 228.
11 A. W. Burgstahler and L. C. Nordin, *J. Am. Chem. Soc.*, 1961, **83**, 198.

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