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AZO ANIONS IN SYNTHESIS. PT 1. t-BUTYLHYDRAZONES AS ACYL-ANION EQUIVALENTS

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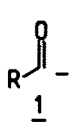
Abstract - The lithium salts of aldehyde t-butylhydrazones react with electrophiles (aldehydes, ketones, alkyl halides, crotonates) to form C-trapped t-butylazo-compounds; tautomerisation and hydrolysis gave α-hydroxy ketones, ketones, and γ-keto esters in good yield, thereby providing a convenient new acyl-anion equivalent. Reaction of these lithium salts with aldehydes and ketones, followed by elimination provided a new route to azo alkenes.

Operational equivalents of the acyl-anion 1 are widely used in organic synthesis, although frequently difficulties arise during the removal of the anion stabilizing auxiliary.[1] This is often a problem with the dithiane sequence based on 2. As an alternative to existing methods which might avoid some of these problems we have examined the chemistry of azo anions, which are readily obtained by deprotonation of hydrazones. Whilst the deprotonation of dialkyl-[2] and arylsulphonyl-hydrazones[3] at the α-carbon atom as 3 is well known, the azo anions derived from alkylhydrazones have not previously been investigated for synthetic purposes. We have shown, in communication form,[4,5] that these azo anions derived from t-butyl hydrazones reacted with electrophiles (aldehydes, ketones, alkyl halides, crotonates) forming C-trapped t-butylazo compounds; tautomerisation and hydrolysis gave ketonic products in good yields, thus illustrating the use of t-butylhydrazones as acyl-anion equivalents. In this article we present an extended description of this work.



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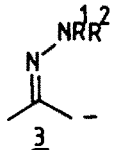

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The t-Butylhydrazones 4a-j were prepared in good to high yield from t-butylhydrazine hydrochloride and carbonyl compounds (Table 1). As these hydrazones were found to be unstable to chromatography they were purified by distillation. They were stored in the absence of light and oxygen to avoid auto-oxidation to azo-peroxides.[6]

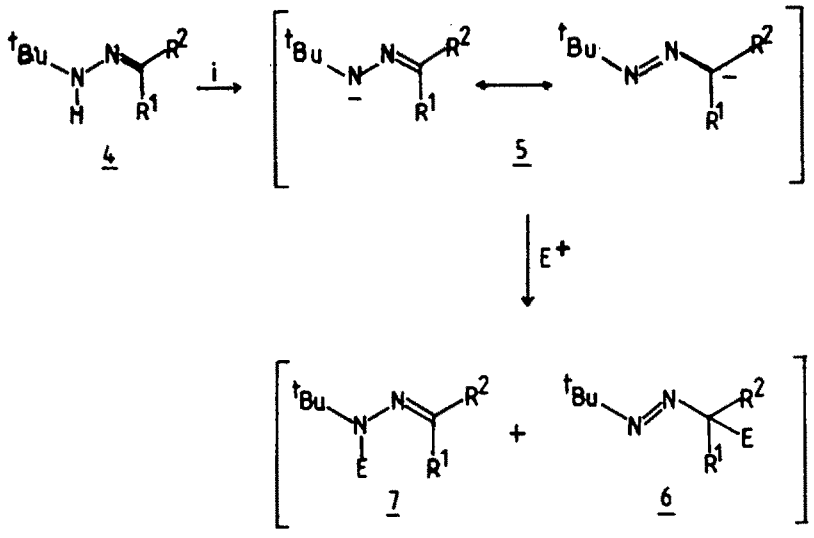
4	R^1	R^2	Yield(%)	b.p.°C	Approx. isomer ratio E/Z
a	H	H	61	68-70 (230 mmHg)	-
b	Me	H	68	41-44 (34 mmHg)	60:40
c[α]	Me	Me	75	40-41 (15 mmHg)	-
d	Et	H	74	78-79 (61 mmHg)	70:30
e[β]	n-Pr	H	77	74 (15 mmHg)	70:30
f	i-Pr	H	73	59.5-61.5 (18 mmHg)	93:7
g	n-Bu	H	88	70-72 (14 mmHg)	75:25
h	$-(CH_2)_5-$		54	104-106 (15 mmHg)	-
i	Ph	H	85	91-93 (1.3 mmHg)	>95:5
j	n-C_7H_{15}	H	58	151-5 (14 mmHg)	85:15

α = see ref. 7

β = see ref. 8

Table 1

Treatment of the t-butylhydrazones 4 with alkyl lithium or lithium di-isopropylamide (THF,0°) gave the azo stabilized anion 5 which is an ambident nucleophile with the possibility of N or C reaction towards electrophiles (E^+). It was known that the azo anions derived from methylhydrazones[9] and phenylhydrazones[10] react with alkyl halides principally on nitrogen. Despite the known reactiviy of t-butylhydrazone anions with silyl fluorides[11] to give N-silylated hydrazones we found that, for most electrophiles, the steric effect of the t-butyl group directed reaction along the desired C-addition pathway to give t-butylazo products 6 (Scheme 1).



Reagents: (i) n-BuLi or $LiN(i\text{-}Pr)_2$

Scheme 1

Reaction of the t-butylazo anions 5 with alkyl halides.

Initially the t-butylazo anion 5h [from cyclohexanone t-butylhydrazone 4h] was quenched (-30° for 3h.) with n-butyl iodide to give the stable t-butylazo species 6h (E=n-Bu, 74%). The azo anions from aldehyde t-butylhydrazones reacted similarly. Thus treatment of 5b with benzyl bromide gave 6b(E=CH_2Ph, 90%) and 5e with trimethylsilyl chloride gave 6e (E=TMS, 75%).

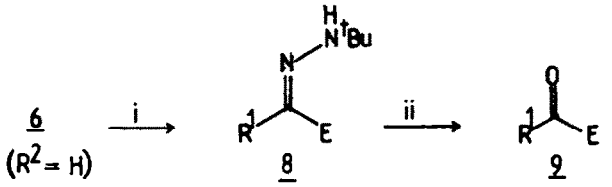
The steric bulk of the alkyl halide electrophile was also found to be an important factor. Thus the azo anion 5e could be quenched with methyl iodide to yield the isolated N-methylhydrazone 7e (E=Me, 71%). In a separate study the ratio of C:N alkylation of the azo anion 5j with methyl iodide (13:87), ethyl iodide (80:20), and n-propyl iodide (87:13) was calculated from the 300MHz ^{1}H n.m.r. spectra of the crude alkylation product (Table 2). With sterically demanding electrophiles, e.g. iso-propyl iodide, the t-butylhydrazones were largely recovered unchanged. Presumably they resulted from a basic reaction of the azo anion with the electrophile or from unreacted starting material. Increasing the reaction time did not improve the yield of C-alkylated product.

Characteristic Chemical Shift (δ p.p.m.)/(Relative Intensity)

RI	N-alkylated	C-alkylated	Recovered 4j
MeI	2.6(87)	3.4(13)	-
EtI	3.0(20)	3.15(80)	(trace)
n-PrI	2.85(11)	3.2(78)	6.5, 7.1 (11)
i-PrI		3.0(37)	6.5, 7.1 (63)

Table 2

The t-butylazo products 6 derived from aldehyde t-butylhydrazones could be tautomerised (TFA, 20°, 6h.) to their corresponding hydrazone forms 8 which could then be trivially hydrolysed to ketones 9 [(15-83%), Scheme 2, Table 3]. The results indicate that steric crowding of the C-alkylation pathway [from either the azo anion 5 or the alkyl halide] leads to diminished yields of ketone 9 products. This methodology offers an attractive one pot ketone synthesis via an acyl-anion equivalent.



Reagents: (i) TFA, 20°, 6h.; (ii) $(CO_2H)_2$, H_2O, Et_2O, N_2, 14h.

Scheme 2

Hydrazone 4	Alkyl halide E^+	Product 9 (%)
b	n-$C_{16}H_{33}I$	68
b	$PhCH_2Br$	67
e	n-$C_7H_{15}I$	48
e	$PhCH_2Br$	71
f	n-$C_7H_{15}I$	15
f	$PhCH_2Br$	74
i	n-$C_7H_{15}I$	83
i	$PhCH_2Br$	72
j	MeI	<5
j	EtI	41
j	n-PrI	53
j	i-PrI	24
j	n-BuI	39

Table 3

Although the tautomerisation of the azo species 6 (R^2=H) to its hydrazone form 8 could be achieved under acidic conditions, the corresponding basic tautomerisation could not be quantitatively achieved. Thus when the azo species 6b (E=CH_2Ph) was treated with n-butyl lithium and deuterium oxide in sequence followed by an aqueous (H_2O) work up, the product contained mostly the fully protonated azo species 6b (E=CH_2Ph) with only minor amounts of the hydrazone 8b (E=CH_2Ph).

Formaldehyde t-butylhydrazone 4a was shown to be an operational equivalent of the carbonyl dianion 10. Thus the azo anion 5a was quenched with an alkyl halide and the resulting azo product 6a purified by chromatography. Tautomerisation (TFA) followed by a basic wash ($NaHCO_3$, sol^n.) gave the hydrazone 8a which was treated with methyl lithium and the second alkyl halide in sequence. Standard tautomerisation and hydrolysis gave the ketone products (Scheme 3).

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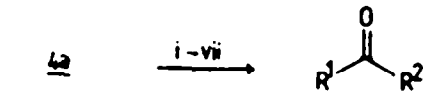


Reagents: (i) MeLi; (ii) R^1X; (iii) TFA, then $NaHCO_3$ wash; (iv) MeLi; (v) R^2X; (vi) TFA; (vii) $(CO_2H)_2$, H_2O, Et_2O, N_2, 20°, 14h.

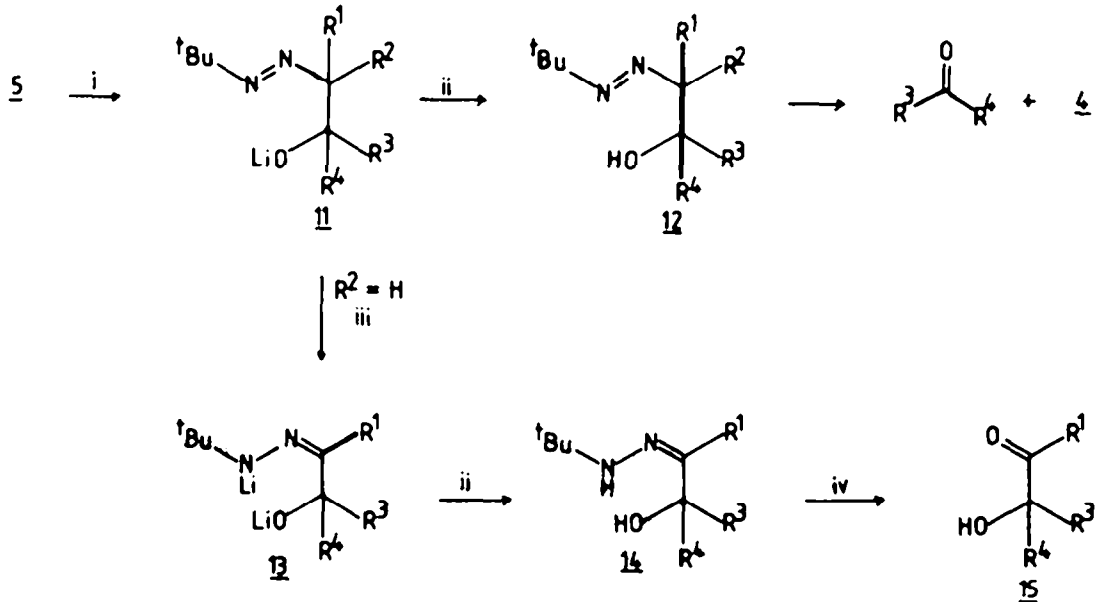
Entry	R^1X	R^2X	Yield (%)
1	n-BuI	$PhCH_2Br$	45
2	$n\text{-}C_7H_{15}I$	$PhCH_2Br$	32

Scheme 3

Reaction of the t-butylazo anions 5 with carbonyl compounds.

The azo anions 5 could be quenched at 0° with carbonyl compounds (ketones, aldehydes) to the azo alkoxides 11 which on protonation gave unstable azo alcohols 12. These azo alcohols 12 reverted to the parent hydrazone 4 and carbonyl compound on standing. Upon treatment of the alkoxide 11 (from an aldehyde t-butylhydrazone 4) with a further portion of n-butyl lithium (1.4 equiv.) in situ followed by a quench with water, the hydroxy hydrazones 14 were cleanly obtained. The tautomerisation and quenching (11→14) were essentially quantitative as judged by the 300 MHz ^1H n.m.r. spectra of 14 (R^1=Me; R^3,R^4=H,Ph) [this tautomerisation procedure was not effective for the non hydroxylated azo species 6]. The hydroxy hydrazones 14 were smoothly hydrolysed to the α-hydroxy ketones 15 (40-95%, table 4, Scheme 4). These results indicate that azo anion methodology offers a convenient synthesis of acyloins.

With enolisable carbonyl electrophiles (e.g. Acetophenone, octan-2-one, cyclohexonone) the yields of isolated acyloins 15 decreased, presumably as a result of a basic reaction of the azo anion with electrophile. Attempts to change the reaction conditions by lowering the temperature at which the carbonyl species was added, or by changing from lithium to a different counter ion (e.g. Mg^{2+}, Zn^{2+}, etc.) did not raise acyloin 15 yields in these cases.



Reagents: (i) $R^3.CO.R^4$, 0°; (ii) H_2O; (iii) n-BuLi, 0°, 30-60 min.; (iv) $(CO_2H)_2$, H_2O, Et_2O, or H_3PO_4, H_2O, Et_2O, N_2, 1-16h.

Scheme 4

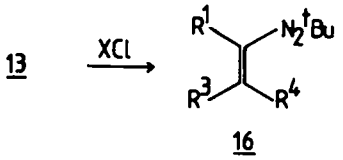
Hydrazone (4)	Electrophile $R^3.CO.R^4$ R^3	R^4	Product 15 (%)
b	H	n-C_7H_{15}	60
b	H	Ph	55
b	Me	n-C_6H_{13}	44α
b	Me	Ph	43β
d	-$(CH_2)_5$-		56
d	H	Ph	66
e	H	n-Pr	62
e	Me	Me	45
e	H	Ph	80
f	-$(CH_2)_5$-		40
f	H	Ph	95
i	Me	Me	-

α Octan-2-one (23%) recovered

β Acetophenone (32%) recovered

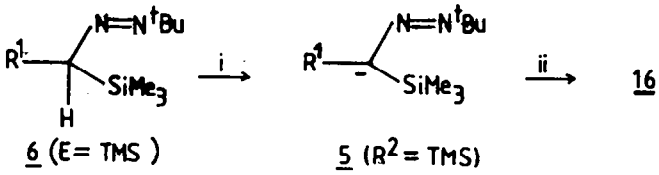
Table 4

Reaction of t-butylazo anions 5 with carbonyl compounds was also used to provide two novel routes to t-butylazo alkenes, which form a previously unknown class of azo alkenes. Treatment of the dianions 13 with diethyl chlorophosphate, trimethylsilyl chloride, thionyl chloride or phosgene gave the azo alkene 16 (Scheme 5). Alternatively 1-trimethylsilyl-t-butylazo alkanes 6 (R^1=H, E=TMS) could be deprotonated (n-butyl lithium, 0°) to give the azo anion 5 (R^2=TMS) which upon quenching with a carbonyl species ($R^3.CO.R^4$) gave the azo alkene 16 (Scheme 6). This second method worked well for the formaldehyde derivative (R^1=H), poorly for the acetaldehyde derivative (R^1=Me) and failed for large alkyl groups, demonstrating again the sensitivity to steric effects of azo anions.



Entry	X	R^1	R^3	R^4	Yield 16 (%)	E:Z ratio †
1	Me_3Si	Me	Ph	H	54	ca 1.2:1
2	$(EtO)_2PO$	Me	Ph	H	48	ca 1:1
3	ClCO	i-Pr	Ph	H	65	ca 1:9
4	ClSO	i-Pr	Ph	H	74	ca 1:9

Scheme 5

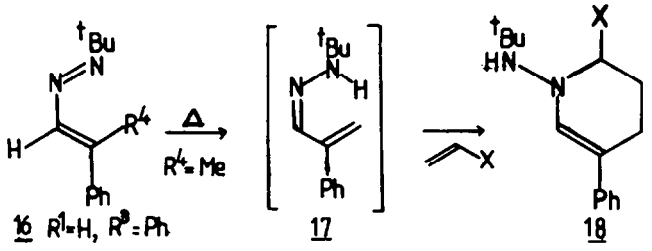


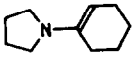
Reagents: (i) n-BuLi, 0°; (ii) $R^3.CO.R^4$

Entry	R^1	R^3	R^4	Yield 16 (%)	E:Z ratio †
1	Me	Ph	H	15	-
2	H	Ph	H	70	ca 3:4
3	H	Ph	Me	73	ca 1:3
4	H	-$(CH_2)_5$-		68	-

Scheme 6

The azo alkene products could be tautomerised (CH_3CO_2H, 20°, 16h.) and hydrolysed to α,β-unsaturated carbonyl compounds as exemplified by the preparation of 1-formylcyclohex-1-ene (37%) from 16 (R_1 = H, R_2,R_4 = $-(CH_2)_3-$). Previous reports[12,13] of azo alkenes had described them as extremely reactive dienes in Diels-Alder reactions. We found that the t-butylazo alkenes 16 did not react with either electron-rich of electron-deficient dieneophiles, unless a sigmatropic rearrangement to an α,β-unsaturated hydrazone, e.g. 17, could occur (Scheme 7), when it was found that the hydrazone form reacted to yield the N-t-butylaminotetrahydropyridine 18.

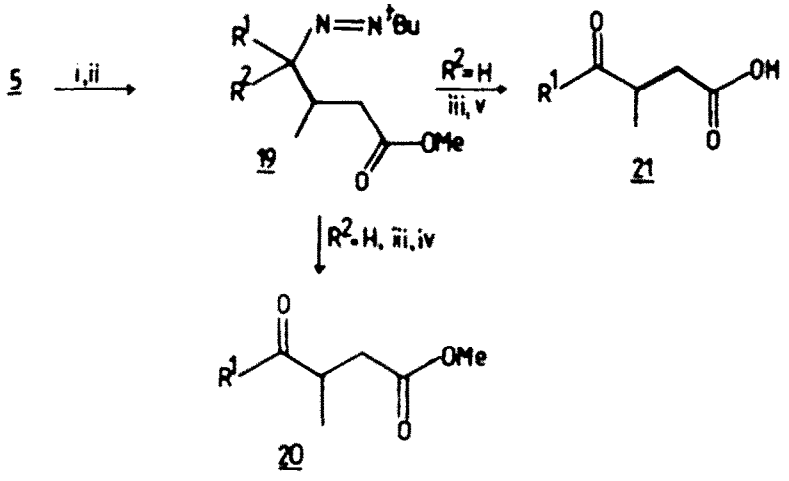


R^4		Temp./°C	Time/h.	Result
H	$EtO.CH=CH_2$	33	15	No reaction
H	Dihydropyran	86	16	No reaction
H	$CH_2=CHCN$	77	16	No reaction
Me	$CH_2=CHCN$	77	50	18 (X-CN) 12%
				16 (R^4=Me) 71%
Me		111	15	No reaction

Scheme 7

Reaction of the t-butylazo anion 5 with Michael electrophiles

The reaction of the azo anions 5 with Michael type electrophiles was examined. Thus treatment of the azo anion 5c or 5h with methyl crotonate (-78°, 30 min) gave, upon acid quenching, the stable t-butylazo esters 19c (58%) and 19h (50%) respectively. A similar reaction with the azo anion from aldehyde t-butylhydrazones, gave upon tautomerisation (TFA, 20°, 5h.) and hydrolysis of the derived azo ester 19, the γ-keto-esters 20 and γ-keto-acids 21 (47-76%, Scheme 8, table 5). As in the case of quenching by carbonyl electrophiles, methyl crotonate may act as both a proton source and a Michael electrophile for the azo anion 5. Other α,β-unsaturated compounds such as methyl acrylate, acrylonitrile or methyl β,β-dimethylacrylate were tried as electrophiles for the azo anions 5; these reagents gave negligible yields of C-addition products. Azo ester and azo nitriles however were formed[8] more efficiently by a thermal ene reaction of aldehyde t-butylhydrazones 4 with methyl acrylate or acrylonitrile.



Reagents: (i) Methyl crotonate; (ii) HOAc or TFA (1 equiv.); (iii) TFA, 5h, 20°, N_2; (iv) $(CO_2H)_2$, H_2O, Et_2O, 12h, 20°; (v) aq. 2M HCl, THF (1:1), reflux, 15h.

Scheme 8

Hydrazone 4	Product (%)
c	19c (58)
h	19h (50)
b	20b (58)
g	20g (60)[a]
f	19f (55); 21g (47)[β]
j	20j (50)
i	19i (68); 21i (47)[β]

a If a deficiency of methyl crotonate (0.5 equiv.) was used in this reaction, then the yield of 20g was 76% based upon methyl crotonate.

β The hydrazone forms of 19f and 19i proved resistant to hydrolysis at 20°. γ-Ketoacids 21 were isolated under more forcing hydrolysis [2M HCl in H_2O: THF (1:1), reflux, 15h.].

Table 5

Reaction of the t-butylazo anions 5 with other electrophiles

Ethyl glyoxylate t-butylhydrazone 22 reacted with alkyl lithium (1 equiv.) and methyl iodide in sequence to yield ethyl pyruvate t-butylhydrazone 23 (59%). Alternatively, the azo anion 5e could be quenched with methyl chloroformate to yield methyl 2-oxopentanoate t-butylhydrazone 24 (36%). However conditions for the successful hydrolysis of either 23 or 24 to stable α-keto esters or acids could not be found.

Epoxides were also tried as electrophiles for the azo anions 5 but no products 6 derived from epoxide opening by 5 could be detected.

In summary the azo anions derived from t-butylhydrazones represent useful and convenient alternatives to the currently used acyl-anion equivalents.[1]

GENERAL EXPERIMENTAL

Standard laboratory practice as previously described[14] was observed. All ^1H NMR spectra were recorded at 300 MHz upon a Bruker WH 300 NMR spectrometer using deuteriochloroform as solvent referenced to residual $CHCl_3$ = 7.27 p.p.m. unless otherwise stated. Coupling constants J were measured to the nearest (±)0.5Hz. All ^{13}C NMR spectra were recorded at 62.85 MHz or 75.4 MHz on either a Bruker AM 250 or Bruker WH 300 spectrometer respectively, using deuteriochloroform as solvent, referenced to $CDCl_3$ = 77.00 p.p.m. unless otherwise stated. Some ^{13}C peaks (especially in the case of geometric isomers) are unresolved. Only selected I.R., ^1H, and ^{13}C NMR signals are assigned. Accurate mass measurements were recorded from the electron impact (E.I.) mode only. Compounds reported in tables but not described in the experimental section gave satisfactory spectral and analytical data consistent with their structures; this data has been omitted in order for brevity in the presentation of this manuscript.

Preparation of t-Butylhydrazones 4. The procedure for the preparation of pentanal t-butylhydrazone (4 g) is typical. To t-butylhydrazine hydrochloride (62.6 g, 0.50 mol) and sodium hydroxide (20.0 g, 0.50 mol) in water (200 ml) was added acetic acid (5 ml, 0.09 mol) and pentanal (60 ml, 0.56 mol). The solution was stirred under an inert atmosphere. After 2 h the layers were separated, the aqueous layer extracted with diethyl ether (2 x 50 ml), the combined organic layers washed with brine, dried (Na_2SO_4), filtered and concentrated. Distillation from sodium hydroxide and calcium hydride gave the title hydrazone (4 g) as a mixture of isomers (E: Z - 3:1) (68.7 g, 88%); b.p. 70-72°/14 mm Hg; ν_{max} (film) 3235 w, 2960 s, 2930 s, 2875 s, 2865 s, 1467 m, 1452 m, 1387 m, 1370 m, 1234 m, 1216 m, and 1097 m cm^{-1}; δH 0.90, 0.93 (3H, 2 x t, J 7Hz, 5-CH_3), 1.16, 1.19 (9H, 2 x s, t-Bu), 1.19-1.55 (4H, m, 3,4-CH_2), 2.04, 2.18 (2H, 2 x dt, J 5Hz, 7Hz, 2-CH_2), 3.65 (1H, br, NH) and 6.48, 7.01 (1H, 2 x t, J 5Hz, 1-CH); δC 13.12 (q, 5-CH_3), 21.53, 21.85 (2 x t, 4-CH_2), 24.83, 26.16 (2 x t, 3-CH_2), 27.69, 27.83 (2 x q, C(CH_3)$_3$), 28.50, 31.25 (2 x t, 2-CH_2), 52.27, 52.36 (2 x s, CMe_3), and 140.54, 141.15 (2 x d, 1-CH); m/e (E.I.) 156 (M^+, 14%), 141 (100), 58 (51), 57 (27), and 41 (19); [Found C: 69.3; H: 13.0, N: 17.7% $C_9H_{20}N_2$ requires C: 69.2, H: 12.9, N: 17.9%].

Preparation of 1-n-Butyl-1-t-butylazocyclohexane 6h (E = n-Bu). Cyclohexanone t-butylhydrazone 4h (0.864 g, 5.0 mmol) was dissolved in THF (30 ml) and the solution cooled to -40°. Methyl lithium (5.5 mmol) was added and the solution stirred for 20 min. 1-Iodobutane (7.5 mmol) was added, the solution warmed to -30° and stirred for 3 h. Acetic acid (15 mmol) was added, then light petroleum (60 ml). The organic layer was passed through flash silica (10 g) using light petroleum (100 ml) as eluant. Evaporation and column chromatography on flash silica gel (50 g, using light petroleum as eluant) gave the title compound 6h (E = n-Bu) (0.826 g, 74%) as an oil; t.l.c. (light petroleum) Rf 0.3; ν_{max} (film) 2975 s, 2930 s, 2865 s, 1452 s, 1388 m, 1382 m, 1362 s (t-Bu), 1229 m, 1210 m, and 738 m cm^{-1}; δH 0.85 (3H, t, J 7Hz, CH_3), 1.01-1.51 and 1.88-1.93 (16H, m, 8 x CH_2), 1.19 (9H, s, t-Bu); δC 14.00 (q, Me), 22.27, 23.42, 24.80, 26.21, 34.04, 38.57 (6 x t, CH_2), 26.92 (q, CMe_3), 66.48 and 69.12 (2 x s, C(1) and CMe_3); m/e (NH_3 C.I.) 225 (MH^+, 100%), and 35 (93).

Preparation of 2-(t-Butylazo)-1-phenylpropane 6b (E = CH_2Ph). Acetaldehyde t-butylhydrazone 4b (1.14 g, 10.0 mmol) was dissolved in THF (10 ml) at 0°. n-Butyl lithium (11.0 mmol) was added over 5 min, the solution stirred for 10 min, then cooled to -78°. Benzyl bromide (12.0 mmol) was added, the solution slowly warmed to 25° over 3 h, then stirred at 25° for 18 h. The mixture was evaporated, the residue dissolved in diethyl ether (200 ml), washed with water (2 x 100 ml), dried, filtered and evaporated to yield crude 6b (E = CH_2Ph) (2.45 g). Purification by flash chromatography [(80 g silica), dichloromethane: light petroleum (0:1-1:1)] gave the title compound 6b (E = CH_2Ph) (1.84 g, 90%); as an oil; t.l.c. [dichloromethane: light petroleum (1:1)] Rf 0.7; ν_{max} (film) 3085 w, 3060 m, 3030 m, 2970 s, 2930 s, 2865 m, 1945 w, 1870 w, 1800 w, 1605 m, 1585 w, 1495 m, 1473 m, 1455 s, 1385 w, 1360 s, 1255 w, 1227 m, 1210 m, 1113 w, 1030 m, 908 w, 845 w, 770 w, 740 s, and 700 s cm^{-1}; δH 1.23 (9H, s, CMe_3), 1.33 (3H, d, J 6.5Hz, 3-H), 3.00-3.07 and 3.19-3.26 (2H, AB part of ABX, 1-H), 3.78-3.89 (1H, m, 2-H), and 7.27-7.40 (5H, m, Ph-H); δC 18.50 (q, CH_3) 27.00 (q, CMe_3), 41.38 (t, CH_2), 66.36 (s, CMe_3), 73.53 (d, CHN_2), 125.93, 128.05, 129.54 (3 x d, phenyl CH) and 138.76 (s, phenyl-ipso-C); λ_{max} 352 nm; m/e (NH_3 C.I.) 205 (MH^+, 100%), and 91 ($C_7H_7^+$, 10); (E.I.) 204 (M^+, 6%), 189 (20), 91 (100), and 57 (90) [Found M^+ 204.1626. $C_{13}H_{20}N_2$ requires 204.1626].

Preparation of (±)-1-t-Butylazo-1-trimethylsilylbutane 6e (E = $SiMe_3$). n-Butanal t-butylhydrazone 4e (1.42 g, 10.0 mmol) was dissolved in THF (20 ml) at 0° and treated with n-butyl lithium (10.0 mmol). After 10 min., trimethylsilyl chloride (2 eq) was added and the reaction mixture allowed to warm to room temperature. After 1 h, the product was concentrated carefully (<5°) and distilled to give the title coupound 6e (E = $SiMe_3$) (1.58 g, 75%); b.p. 104-106° at 46 mm Hg; t.l.c. [dichloromethane] decomposes; ν_{max} (film) 2965 s, 2940 m, 2910 m, 2875 m, 1465 m, 1456 m, 1360 m, 1251 s, 903 m, 860 s, 840 s, and 702m cm^{-1}; δH 0.01 (9H,s, $SiMe_3$), 0.87 (3H, t, J 7Hz, 4-CH_3), 1.04-1.14 (2H, m, 3-CH_2), 1.18 (9H, s, t-Bu), 1.62-1.74 (1H, m, CHH-CHNSi), 2.21-2.33 (1H, m, CHH-CHNSi), and 3.42 (1H, dd, J 14.5, 3Hz, CHNSi); m/e (NH_3 C.I.) 215 (NH^+, 100%), 143 (30), 90 (36), 74 (65), 73 (22), and 58 (12); m/e (E.I.) 214 (M^+, 13%), 199 (5), 73 (100), 57 (86), and 41 (31); [Found M^+ 214.1865, $C_{11}H_{26}N_2Si$ requires 214.1865].

Reaction of the anion of Butanal t-butylhydrazone 5e with methyl iodide. To butanal t-butylhydrazone 4e (1.44 g, 10.0 mmol) in THF (15 ml) was added n-butyl lithium (1.05 eq, 10.5 mmol). After 5 min., the reaction was cooled to -78°, then methyl iodide (1.0 ml, 10.0 mmol) was added and the reaction was allowed to warm slowly to room temperature. After 16 h, water (0.5 ml) was added, the solution dried (sodium sulphate), then light petroleum (60 ml) was added. The solution was filtered through celite and concentrated. Distillation gave (E)-butanal N-t-butyl-N-methylhydrazone 7e (E = Me) (1.12 g, 71%); b.p. 61-2° at 15 mm Hg; t.l.c. [dichloromethane] decomposes; ν_{max} (film) 2990 s, 2870 s, 2790m, 1660w (C=N), 1475 s, 1463 m, 1455 s, 1413 m, 1387 s, 1359 s, 1337 m, 1247 s, 1225 s, 1179 m, 1154 s, 1133 m, 1106 s, 1054 m, 1021 m, 994 m, 965 s, 898 m, and 824 m cm^{-1}; δH 0.99 (3H,t,J 7Hz, 4-CH_3),1.19 (9H, s, t-Bu), 1.525 (2H, ca sextet, J 7.5Hz, 3-CH_2), 2.21 (2H, t of d, J 7.5, 5Hz, 2-CH_2), 2.51 (3H, s, N-CH_3), and 6.88 (1H, t, J 5Hz, =CH); m/e (E.I.) 156 (M^+, 32%), 141 (100), 100 (9), 85 (14), 72 (51), 71 (38), 70 (26), 57 (77), 56 (30), and 41 (41); [Found M^+ 156.1626, $C_9H_{20}N_2$ requires 156.1626].

A study of the alkylation of azo anion 5j. Octanal t-butylhydrazone 4j (0.99 g, 5.0 mmol) was dissolved in THF (5 ml) at 0°. n-Butyl lithium (5.6 mmol) was added over 5 min., the solution stirred for 10 min., then cooled to -78°. The alkyl iodides [8.0 mmol; (a) Methyl iodide, (b) ethyl iodide, (c) n-propyl iodide, and (d) iso-propyl iodide] were added [in separate experiments], the solution warmed to 25° over 3 h, then stirred for 18 h. A portion of the product was quenched with water, extracted into diethyl ether, dried, filtered, and evaporated. Direct ^{1}H n.m.r. analysis indicated the ratios of N-alkyl, C-alkyl, and recovered 4j products [Table 2]. These ratios were determined by integration of the N-alkyl (CH_2N), C-alkyl (CHN_2), and recovered 5j (HC=N) resonances.

Acidic tautomerisation of the t-butylazo species 6b (E = CH_2Ph) to its hydrazone form 8b (E = CH_2Ph). The azo species 6b (E = CH_2Ph) (211 mg, 1.03 mmol) was dissolved in dichloromethane (8 ml) and TFA (2 ml) and stirred for 18 h at 25°. Evaporation of the solvent gave the hydrazone form 8b (E = CH_2Ph) as a mixture of E, Z-isomers without any unreacted azo species 6b (E = CH_2Ph), δH (60MHz) for E-form 1.35 (9H, s, CMe_3), 2.0 (3H, s, 3-H), 3.65 (2H, s, 1-H), 7.2 (5H, br s, Ph-H), for Z-form 1.3 (9H, s, CMe_3), 2.15 (3H, s, 3-H), 3.85 (2H, s, 1-H), and 7.2 (5H, br s, Ph-H).

Oxalic acid (3 g), water (15 ml) and diethyl ether (25 ml) were added and the suspension stirred under nitrogen for 18 h. Diethyl ether (100 ml) was added, the organic layer separated, washed with saturated aqueous $NaHCO_3$ solution, dried, filtered, and evaporated. Purification by p.l.c. (2 x 20 x 20 x 0.1 cm silica plates, dichloromethane) gave phenylacetone 9b (E = CH_2Ph) (95 mg, 69%), as an oil, t.l.c. [diethyl ether: petroleum (2:3)] Rf 0.4; ν_{max} (film) 1713 s (C=O), 734 s (Ph-H), and 699 s (Ph-H) cm^{-1}; δH (60 MHz) 2.15 (3H, s, 3-H), 3.66 (2H, s, 1-H), and 7.22 (5H, s, Ph-H); m/e (E.I.) 134 (M^+, 21%), 91 ($C_7H_7^+$, 65), and 43 (CH_3CO^+, 100).

Preparation of Ketones 9 from aldehyde t-butylhydrazones 4. The following procedure for the preparation of phenylacetone 9b (E = CH_2Ph) from acetaldehyde t-butylhydrazone 4b is typical of all ketone 9 preparations.

Acetaldehyde t-butylhydrazone 4b (1.14 g, 10.0 mmol) was dissolved in THF (10 ml) at 0°. n-Butyl lithium (11.0 mmol) was added over 5 min., the solution stirred for 10 min., then cooled to -78°. Benzylbromide (12.0 mmol) was added, the solution warmed to 25° over 3 h then stirred for 18 h. TFA (1 ml) was added, the solution stirred for 16 h, then evaporated. The residue was dissolved in diethyl ether (30 ml), and water (20 ml), oxalic acid (3 g) added and the mixture stirred for 1 d. Ether (200 ml) was added, the organic layer separated, washed with saturated $NaHCO_3$ solution (50 ml), dried, filtered, and evaporated to yield a crude product (1.81 g). Purification of a sample (212 mg) by p.l.c. [2 x 20 x20 x 0.1 cm plates, dichloromethane] gave phenylacetone 9b (E = CH_2Ph) (106 mg, 67%), t.l.c., n.m.r. as before.

Attempted basic tautomerisation of the t-butylazo species 6b (E = CH_2Ph) to its hydrazone form 8b (E = CH_2Ph). The t-butylazo product 6b (E = CH_2Ph) (246 mg, 1.21 mmol) was dissolved in THF (5 ml) [or 1,2-dimethoxyethane (5 ml)] at 0°. n-Butyl lithium (1.60 mmol) was added over 5 min., the solution stirred for 20 min., then quenched with D_2O (0.25 ml). The solvent was evaporated, the residue extracted into diethyl ether (200 ml), washed with water (50 ml), dried, filtered, and evaporated. T.l.c. (dichloromethane) indicated the presence of the azo species 6b (E = CH_2Ph) Rf 0.80, ca 50%. ^{1}H n.m.r. (60 MHz) analysis indicated the presence of the fully protonated azo species 6b (E = CH_2Ph), δH 3.8 (1H, m, 2-H).

Preparation of Benzyl n-heptylketone 9j; (E = CH_2Ph) from formaldehyde t-butylhydrazone (4a). Formaldehyde t-butylhydrazone 4a (1.00g, 10.0 mmol) was dissolved in dry THF (20 ml) at 0°. Methyl lithium (11 mmol) was added over 5 min., the solution stirred for 15 min., cooled to -70° and stirred for 15 min. n-Heptyl iodide (11 mmol) was then added, the solution stirred for 1 h at -70° then warmed slowly to 20° and stirred for 16 h. The solution was evaporated, partitioned between diethyl ether (200ml) and water (100ml), the organic layer dried, evaporated and purified by column chromatography [flash silica, (50 g) using petroleum/dichloromethane as eluant] to yield a crude product (~ 85% yield). The azo compound was tautomerisated by stirring with TFA (20 mmol) in benzene (10 ml) for 5 h under nitrogen. The solvent was evaporated and the residue extracted into diethyl ether (200ml) and saturated aqueous $NaHCO_3$ (100 ml). The organic layer was dried (Na_2SO_4) filtered and evaporated to yield octanal t-butylhydrazone (4j) (ca 80%). This reagent was used without further purification in the method described earlier. Thus reaction with methyl lithium benzyl bromide, TFA, and aqueous oxalic acid in sequence gave benzyl n-heptylketone 9j (E = CH_2Ph) (698 mg, 32%) as an oil,t.l.c. [(dichloromethane: petroleum (1:1)] Rf 0.6, ν_{max} (film) 1715 s (C=O) and 700 s cm^{-1}; δH 0.88 (3H, ca t, J 7Hz, Me), 1.24 (8H, br s, $(CH_2)_4Me$), 1.5-1.65 (2H, m, CH_2CH_2CO), 2.45 (2H, t, J 7.5Hz, RCH_2CO), 3.69 (2H, s, CH_2Ph), and 7.2-7.4 (5H, m, Ph-H), m/e (E.I.) 218 (M^+, 2%), 127 (70), and 57 (100). A similar sequence using 4a, n-butyliodide and benzyl bromide gave benzyl n-butylketone 9g (E = CH_2Ph) (45%).

Preparation of (±)-2-t-Butylazo-2-methyldecan-3-ol (12, R^1 = R^2 = Me, R^3 = H, R^4 = n-C_7H_{15}). Acetone t-butylhydrazone 4c (1.28 g, 10.0 mmol) was dissolved in THF (10 ml) at 0°. n-Butyl lithium (11.0 mmol) was added dropwise over 5 min., the solution stirred for 10min., then quenched with octanal (12.0 mmol). The solution was evaporated, dissolved in diethyl ether(100 ml), washed with aqueous orthophosphoric acid(5%, 20 ml), dried, filtered, and evaporated to yield the crude title azo-alcohol (12, R^1 = R^2 = Me, R^3 = H, R^4 = n-C_7H_{15}) (1.97 g, < 77%) as an oil; ν_{max} (film) 2925 s, 1122 m, and 1075 m cm^{-1}, δH (60 MH_2) (3H, t, J 5Hz, 10-H), 1.17 (15H, 2 x s, t-Bu, CH_3), 1.30 (12H, br s, 4,-9-H), 2.91 (1H, br, OH), and 3.64 (1H, br, CHOH); m/e (F.I.) 256 (M^+). The sample decomposed upon standing in $CHCl_3$ solution at 20°.

Basic tautomerisation of the azoalkoxide 11 (R^1 = R^3 = H, R^2 = Me, R^4 = Ph) to its hydrazone anion form 13 (R^1 = Me, R^3, R^4 = H, Ph). Acetaldehyde t-butylhydrazone 4b (1.14 g, 10.0 mmol) was dissolved in THF (10ml) and the solution cooled to 0° under nitrogen. n-Butyl lithium (11.2 mmol) was added and the solution stirred for 45 min., then quenched with benzaldehyde (11.0 mmol). An aliquot (2.0 ml) was removed, evaporated and partitioned between diethyl ether (50 ml) and water (50 ml). The organic layer was separated, dried, filtered and evaporated to give a crude azo-alcohol (12 R^1 = R^3 = H, R^2 = Me; R^4 = Ph) (ca 90%) as a 2:1 mixture of diastereomers, δH_{max} 1.13 and 1.07 (3H, 2 x d, J 7Hz, MeCH), 1.18 and 1.23 (9H, 2 x s, t-Bu), 2.9-3.0 (1H, br, OH), 3.9-4.0 and 3.7-3.8 (1H, 2 x m, CHN_2), 5.08 and 4.97 (1H, 2 x d, J 4Hz, 7.5Hz, CHPh).

The remaining benzaldehyde quenched product was treated with n-butyl lithium (12.8 mmol),

stirred at 0° for 1 h, and quenched with water (1 ml). The solvent was evaporated, the residue extracted into diethyl ether (100 ml) and water (25 ml), the organic layer separated, dried, filtered and evaporated to give the crude hydrazone 14 (R^1 = Me, R^3, R^4 = H,Ph), δH 1.10 (9H, s, t-Bu), 2.05 (3H, s, $CH_3C{=}N$), 5.45 (1H, s, CHPh), and 7.2-7.4 (5H, m, Ph-H) without any detectable azo-alcohol (12 R^1 = R^3 = H, R^2 = Me, R^4 = Ph).

Preparation of α-Hydroxyketone (15) from an aldehyde t-butylhydrazone 4. The following procedure for the preparation of 1-Hydroxy-1-phenylpropan-2-one (15, R^1 = Me, R^3, R^4 = H, Ph) from acetaldehyde-t-butylhydrazone 4b is typical of all α-Hydroxyketone (15) preparations, except for 3-hydroxy-decan-2-one (15, R^1 = Me, R^3, R^4 = H, n-C_7H_{15}), and 3-hydroxy-3-phenylbutan-2-one (15, R^1 = Me, R^3, R^4 = Me, Ph), where the final hydrazone hydrolysis was achieved with orthophosphoric acid (88%, 1.5 ml) in water (30ml) and diethyl ether (40 ml).

Acetaldehyde t-butylhydrazone (4b, 1.14 g, 10.0 mmol) was dissolved in THF (10 ml) under nitrogen at 0°. n-Butyl lithium (11.0 mmol) was added over 5 min., the solution stirred for 10 min., then quenched with benzaldehyde (12.0 mmol). Further n-butyl lithium (14.0 mmol) was added over 5 min., the solution stirred for 1 h at 0°,cooled to -78°, then quenched with acetic acid: water (1:1) (0.5 ml). The mixture was warmed to 25°, the solvent evaporated and the residue dissolved in dichloromethane (100 ml) and water (50 ml). The organic layer was separated, dried, filtered, and evaporated to yield a crude hydroxyhydrazone. Oxalic acid (3 g), water (30 ml) and diethyl ether (20 ml) were added and the solution stirred under nitrogen for 18 h. Diethyl ether (100 ml) was added, the organic layer separated, washed with saturated aqueous $NaHCO_3$ solution (30 ml), dried, filtered and evaporated to yield crude (15, R^1 = Me, R^3,R^4 = H, Ph) (1.46 g). Purification of a sample (172 mg) by p.l.c. [3 x 20 x 20 x 0.1 cm silica plates, eluant diethyl ether: dichloromethane (2:23)] gave the title compound[15] (15, R^1 = Me, R^3,R^4 = H, Ph) (98 mg, 55%) as an oil; t.l.c. [diethyl ether: dichloromethane (1:9)] Rf 0.6; ν_{max} ($CHCl_3$) 3475 br w (O-H), 3030 w (Ar-H), 3010 w (Ar-H), 2938 w (C-H), 1715 s (C=O), 1495 m (Ar-H), 1360 m (C-H), 1092 m (C-O), 1070 m (C-O), and 703 s (Ar-H) cm^{-1}; δH 2.10 (3H, s, 2-CH_3), 4.31 (1H, d, J 4Hz, OH), 5.11 (1H, d, J 4Hz, CHOH), and 7.32-7.43 (5H, m, ArH); δC 25.21 (q, 3-C), 88.09 (d, 1-C), 127.30, 128.70, 129.97 (3 x d, aryl CH), 137.90 (s, aryl-ipso-C), and 207.08 (s, 2-C); m/e (E.I.)150 (M^+, 2%), 107 (100), 105 (34), 79 (96), 77 (58), and 43 (26%).

Preparation of E, Z-2-(t-Butylazo)-1-phenylpropene (16, R^1 = Me, R^3, R^4 = H, Ph). 4b (10.0 mmol) was dissolved in THF (15 ml) at 0°. n-Butyl lithium (10.0 mmol) was added, the solution stirred for 15 mins., and benzaldehyde (10.0 mmol) added. After 15 mins., n-butyl lithium (12.0 mmol) was added. After 1 h., trimethylsilyl chloride (10.0 mmol, method A), or diethylchlorophosphate (10.0 mmol, method B) was added, the reaction stirred for 3.5 h whilst it warmed to room temperature. Water (0.8 ml) was added, the solution dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography [70 g, using diethyl ether: light petroleum (1:19-1.9) as eluant] gave the title compound (1.11 g, 54%, method A) or (0.98 g, 48%, method B) as a mixture of isomers (E: Z ca 1.2:1); orange oil; t.l.c. [diethyl ether: light petroleum (1:4)] Rf 0.6; ν_{max} (film) 3090 (=C-H), 3062 m, 3031 m, 2986 s, 2929 m, 2871 m, 1692 m, 1602 w (C=C), 1503 m, 1495 m, 1488 m, 1449 m, 1382 m, 1362 m, 1253 m, 1219 m, 1209 m, 1178 m, 1150 m, 1006 m, 923 m, 882 m, 750 s (Ar-H), and 695 s (Ar-H)cm^{-1}; λ_{max} (CH_3CN) 285 nm (ε 1.4 x 10^4); δH 1.29, 1.30, (9H, 2 x s, t-Bu), 1.97, 2.07 (3H, 2 x d, J 1Hz, 3-CH_3), 6.78 (<1H, s, =CH of 1 isomer) and 7.26-7.49, 7.73-7.76 (<6H, m, ArH, =CH of other isomer); m/e (E.I.) 202 (M^+, 6%), 145 (9), 117 (71), 115 (20), 105 (10), 91 (13), 77 (7), 57 (100), and 41 (28); [M^+ found: 202.1469, $C_{13}H_{18}N_2$ requires 202.1470].

Preparation of 3-Methyl-1-phenyl-2-t-butylazobut-1-ene (16, R^1 = i-Pr, R^3, R^4 = H, Ph). 4f (10.0 mmol) was dissolved in THF (15 ml) at 0°. n-Butyl lithium (11.0 mmol) was added, the solution stirred for 10 min., and benzaldehyde (12.0 mmol) added. After 15 min., n-butyl lithium (12.0 mmol) was added. After 15 min. phosgene (13 mmol, solution in toluene, method A) or thionyl chloride (13 mmol, method B) was added, and the reaction warmed to room temperature over 16 h. Water (0.5 ml) and diethyl ether (30 ml) were added, the solution dried (Na_2SO_4), filtered and evaporated. Purification by chromatography [70 g, eluant diethyl ether: light petroleum (1:19-1:9)] and p.l.c. [eluant diethyl ether: light petroleum (1:9)] gave the title azo alkene (1.495 g, 65%, method A) and (1.70 g, 74%, method B), as a mixture of isomers (E: Z ca 1.0:8.5); b.p. 175° at 14 mmHg; t.l.c. [diethyl ether: light petroleum (1:4)] Rf 0.7 (E), 0.6 (Z); ν_{max} (film) 3085 w, 3030 w, 2966 s, 2930 m, 2910 m, 2870 m,1470 m, 1455 m, 1447 m, 1386 m, 1362 m, 1220 m, 1210 m, 757 m, and 696 s cm^{-1}, λ_{max} (CH_3CN) 286 nm (ε 8.5 x 10^3); δH 1.12, 1.24 (6H, 2 x d, J 7Hz, E, Z $CHMe_2$), 1.30, 1.32 (9H, 2 x s, E and Z t-Bu), 3.17, 3.33 (1H, 2 x septet, J 7Hz, E, Z $CHMe_2$), 6.30, 6.63 (1H, 2 x s, E and Z C=CH), 7.23-7.41 and 7.66-7.69 (5H, 2 x m, aryl-H); m/e (E.I.) 230 (M^+, 4%), 145 (M^+-t-BuN_2, 100), 117 (36), 105 (24), 91 (52), 57 (64), and 41 (21); (Found: C, 77.88%; H, 9.82%; N, 12.37%. $C_{15}H_{22}N_2$ requires C, 78.21%; H, 9.63%, and N, 12.16%).

In an n.O.e. experiment irradiation of the vinylic hydrogen of the major isomer δH 6.63 gave n.O.e. of the major $CHMe_2$, δH 3.17 (1.5%), whereas irradiation of the vinylic hydrogen of the minor isomer δH 6.30 gave n.O.e. of the minor $CHMe_2$, δH 3.33 (0.2%).

Preparation of t-Butylazo alkenes via t-butylazo-trimethylsilylmethane (6a, E = TMS). The following procedure for the preparation of E, Z-1-(t-butylazo)-2-phenylethene (16, R^1 = H, R^3, R^4 = H, Ph) is typical of all azo alkene preparations by Peterson olefination methodology, except for (16, R^1 =H, R^3, R^4 = -$(CH_2)_5$-) which was isolated by distillation, b.p. 118° at 15 mmHg.

To formaldehyde t-butylhydrazone 4a (5.01 g, 50 mmol) in THF (50 ml) and diethyl ether (200 ml) was added n-butyl lithium (48 mmol). After 15 min., trimethylsilyl chloride (13 ml, 100 mmol) was added quickly. After 2 h.the solution was filtered, concentrated, dissolved in hexane (150 ml), filtered, and concentrated. Distillation gave t-butylazo-trimethylsilylmethane (6a, E = TMS) (4.52 g, 55%); b.p. 97-9° at 155 mmHg; ν_{max} (film) 2975 s, 2930 s, 2905 s, 2875 s, 1474 m, 1457 m, 1405 m, 1387 m, 1362 s, 1251 s, 1200 m, 1162 m, 991 m, 910 s, 848 s, 760 m, 703 m, and 680 m cm^{-1}; δH 0.09 (9H, s, $SiMe_3$), 1.20 (9H, s, t-Bu), and 3.91 (2H, s, CH_2); m/e (E.I.) 172 (M^+, 2%).

t-Butylazo-trimethylsilylmethane (6a, E = $SiMe_3$) (0.894 g, 5.0 mmol) was dissolved in THF (15 ml) at 0°. n-Butyl lithium (5.5 mmol) was added and the reaction stirred for 10 min. Benzaldehyde (6.0 mmol) was added and the reaction stirred for ½ h, then warmed to R.T..Water (0.5 ml) was added, the solution dried, filtered and concentrated. Chromatography [70 g silica, diethyl ether: light petroleum, (1) (1:19, 200 ml),; (2) (1:9, 200 ml); (3) (3:17, 200 ml)] gave

(E, Z)-1-(t-butylazo)-2-phenylethene (16, R^1 = H, R^2, R^3 = H, Ph) (0.654 g, 70%) as a mixture of isomers (E, Z ~ 3:4); orange oil; t.l.c. [diethylether:dichloromethane (1:4)] Rf 0.7; ν_{max} (film) 3090 w, 3065 w, 3305 m, 2975 s, 2935 m, 2910 m, 2870 w, 1633 w, 1599 w, 1492 w, 1474 w, 1449 m, 1362 m, 955 m, 754 m, and 682 s cm^{-1}; λ_{max} 289 nm (CH_3CN) (ε 1.8 x 10^4); δH (300 MHz, C_6D_6 reference residual C_6D_5H = 7.30 p.p.m.) 1.26 (E), 1.34 (Z) (9H, 2 x s, t-Bu), 6.38, 7.15 (<2H, 2 x d, J 9Hz, (Z)-PhCH=CH-N), 6.96-7.23, 7.88-7.91 (5H, m, ArH) and 7.65, 7.87 (<2H, ABq, J 14Hz, (E)-Ph-CH=CH); m/e (NH_3 C.I.) 189 (MH^+, 100%), 120 (11), 94 (13), 74 (23), 58 (15), and 44 (26); m/e (E.I.) 188 (M^+, 3%), 131 (10), 103 (39), 102 (15), 77 (42), 57 (100), and 41 (63); [Found M^+ : 188.1314, $C_{12}H_{16}N_2$ requires 188.1314].

Preparation of 1-Formylcyclohexene. [16, R^1 = H, R^2, R^3 = $-(CH_2)_4-$] (0.92 g, 5.0 mmol) was stirred in acetic acid (5 ml). After 16 h. the acid was evaporated to yield crude 1-formylcyclohexene t-butylhydrazone which was hydrolysed by the standard oxalic acid-water-diethyl ether system. Purification by p.l.c. [dichloromethane] gave 1-formylcyclohexene (203 mg, 37%); t.l.c. (dichloromethane) Rf 0.5; ν_{max} (film) 2935 m, 2864 m, 2830 w (CHO), 2715 w (CHO), 1690 s (C=O), 1645 m (C=C), 1180 m, and 787 m cm^{-1}; δH 1.62-1.72 (4H, m, 4,5-CH_2), 2.18-2.22, 2.30-2.37 (4H, 2 x m, 3,6-CH_2), 6.79-6.83 (1H, m, 2-CH), and 9.40 (1H, s, CHO); m/e (E.I.) 110 (M^+, 61%), 95 (28), 81 (100), 79 (43), 53 (41), 41 (56), and 39 (50); 2,4-dinitrophenylhydrazone derivative m.p. 218-9°, m/e (E.I.) 290 (M^+, 40%), [Found: 53.74%; H, 4.86%; N, 19.53%, calculated for $C_{13}H_{14}N_4O_4$ C, 53.78%; 4.86%; N, 19.31%].

Thermal reaction between (E, Z)-1-(t-butylazo)-2-phenylpropene (16, R^1 = H, R^2, R^3 = Me, Ph) and acrylonitrile. (16, R^1 = H, R^2, R^3 = Me,Ph) (108 mg, 0.5 mmol) was refluxed in acrylonitrile (6 ml, 90 mmol, b.p. 77°) for 50 h. The sample was concentrated then p.l.c. [2 x 20 x 20 x 0.1 cm plates/eluant diethyl ether: light petroleum (1:4)] gave the starting azoalkene (77 mg, 71%) and (±)-N-(t-butylamino)-2-cyano-5-phenyl-1,2,3,4-tetrahydropyridine (18) (16 mg, 12%); oil; ν_{max} ($CHCl_3$) 3830 br w (N-H), 3085 w (=C-H), 3060 w, 3010 m, 2970 s, 2940 m, 2240 w (C N), 1633 s (C=C), 1599 (ArC=C), 1495 m, 1480 m, 1448 m, 1390 m, 1363 m, 1334 m, 910 m, 866 m, and 696 m cm^{-1}; δH 1.13 (9H, s, t-Bu), 2.23-2.46 (3H, m, 3-CH_2, 4-CHH), 2.63-2.78 (1H, m, 4-CHH), 4.14— 4.18 (1H, m, N-CH-CN), 6.37-6.38 (1H, m, =CH), and 7.13-7.37 (5H, m, ArH); m/e (E.I.) 255 (M^+, 72%), 228 (7), 227 (7), 199 (87), 198 (18), 187 (16), 171 (31), 155 (94), 145 (100), 119 (96), 57 (95), and 41 (87); [Found M^+ 255.1737, $C_{16}H_{21}N_3$ requires 255.1735].

Preparation of Michael adduct (19h). The following procedure for the preparation of methyl 3-(1-t-butylazocyclohexyl)butanoate (19h) from 4h and methyl crotonate is typical of all t-butylazo esters (19).

4h (5.0 mmol) was dissolved in THF (10 ml) at 0° and n-butyl lithium (4.75 mmol) added. The solution was stirred for 10 min., cooled to -78°, methyl crotonate (5.0 mmol) added and the solution stirred for 30 min. Acetic acid (0.5 ml) and light petroleum (25 ml) were added, the solution warmed to room temperature, filtered, and concentrated. Purification by column chromatography [60 g, eluant diethyl ether: light petroleum (1:24-1:9)] and p.l.c. [diethyl ether: light petroleum (1:19)] gave methyl-3-(1-t-butylazocyclohexyl)butanoate (19h) (640 mg, 50%), b.p. 130° at 0.4 mmHg, t.l.c. [diethyl ether: light petroleum (1:4)] Rf 0.6; ν_{max} (film) 2980 s, 2960 s, 2940 s, 2875 m, 1745 s (C=O), 1453 m, 1438 m, 1386 m, 1363 m, 1303 m, 1276 m, 1258 m, 1198 m, 1177 m, and 1021 m cm^{-1}; δH 0.87 (3H, d, J 7Hz, CHMe), 1.20 (9H, s, t-Bu), 1.41-1.60 and 1.96-2.06 (10H, 2 x br, 5 x CH_2), 1.90-1.98 (1H, m, CHHCO$_2$Me), 2.20-2.31 (1H, m, CHMe), 2.53-2.59 (1H, m, CHHCO$_2$Me), and 3.66 (3H, s, CO_2Me); δC 14.18 (q, 3-Me), 26.98 (q, t-Bu), 21.83, 21.92, 25.89, 30.69, 31.85, 35.91 (6 x t, CH_2), 37.65 (d, 3-CH), 51.39 (q, OMe), 67.35, 70.27 (2 x s, CN_2C), and 174.36 (s, C=O);m/e (NH_3 C.I.) 269 (MH^+, 58%),183 (32), 151 (30), 123 (22), 109 (100), 81 (31), 67 (21), 57 (18), and 41 (33); (Found, C, 67.1%; H, 10.4%; N, 10.1%. $C_{15}H_{28}N_2O_2$ requires C, 67.1%; H, 10.5%; N, 10.4%).

Preparation of Methyl 3-methyl-4-oxopentanoate (20b). The following procedure for the preparation of 20b is typical of all γ-keto-esters (20).

4b (5.0 mmol) was reacted with n-butyl lithium (0.95 eq) and methyl crotonate as before to produce crude azo-ester (19b) which was isomerised with TFA and hydrolysed [$(COOH)_2$-H_2O-diethyl ether] as in the general procedure for ketone preparation. Purification by column chromatography and p.l.c. gave Methyl 3-methyl-4-oxopentanoate (20b) (395 mg, 58%); b.p. 131° at 7 mmHg; t.l.c. [diethyl ether: dichloromethane (1:39)] Rf 0.2; ν_{max} (film) 2975 m, 2960 m, 2885 m, 1740 s (C=O, ester), 1715 s (C=O, ketone), 1465 m, 1442 m, 1437 m, 1413 m, 1360 m, 1276 m, 1204 s, 1167 s, 1127 m, 1086 m, 1015 m, and 1011 m cm^{-1}; δH 1.16 (3H, d, J 7Hz, CHMe), 2.23 (3H, s, 5-H), 2.27-2.34, 2.73-2.82 (2H, 2 x m, CH_2CO_2Me), 2.99-3.06 (1H, m, 3-CH), and 3.67 (3H, s, OMe), δC 16.40 (q, Me), 28.22 (q, C(5)), 36.19 (t, C(2)), 42.62 (d, C(3)), 51.54 (q, OMe), 172.58 (s, CO_2Me), and 210.48 (s, C=O); m/e (NH_3 C.I.) 162 (MNH_4^+, 87%), 145 (MH^+, 22), and 35 (100); (E.I.) 144 (M^+ 1%), 113 (15), 102 (12), 87 (18), 84 (12), 60 (24), 59 (19), and 43 (100); [Found C, 58.6%; H, 8.5%/ $C_7H_{12}O_3$ requires C, 58.9%, H. 8.4%].

Preparation of 3,5-Dimethyl-4-oxohexanoic acid (21 f). The general method for the preparation of azo esters (19) was employed for the preparation of 19f from 4f (5.0mmol) and methyl crotonate. (19f) was isomerised (TFA, 20° 5 h) to its hydrazone form but this proved resistant to the hydrolysis at 20°. The crude hydrazone was dissolved in 2M hydrochloric acid: THF (1:1, 20 ml) and refluxed for 15 h. Purification by column chromatography (50 g, diethyl ether) and p.l.c. [diethyl ether: dichloromethane (3:1)] gave the title keto acid (21f) (371 mg, 47%); b.p. 182° at 0.5 mmHg; t.l.c. [diethyl ether: dichloromethane (3:1)] Rf 0.5; ν_{max} (film) 3700-2400 m br, 2980 s, 2940 m, 2882 m, 1715 s (C=O, ketone), 1705 s, (C=O, acid), 1470 m, 1400 m, 1386 m, 1370 m, 1275 m, 1230 m, 1178 m, 1150 m, 1100 m, and 1027 m cm^{-1}; δH 1.09-1.16 (9H, m, 3 x CH_3), 2.30-2.37, 2.78-2.86 (2H, 2 x m, 2-CH_2), 2.81-2.88 (1H, m, 5-CH), 3.12-3.20 (1H, m, 3-CH), and 9.85-10.15 (1H, br, CO_2H); δC 16.92, 18.07, 18.74 (3x q, 3 x Me), 36.83 (t, C(2)), 39.16, 40.21 (2 x d, C(3), C(5)), 178.12 (s, CO_2H), 216.47 (s, C=O); m/e (E.I.) 158 (M^+, 1%), 115 (33), 87 (22), 71 (39), and 43 (100), [Found, C, 60.8%; H, 9.1%, $C_9H_{14}O_3$ requires C, 60.7%: H, 8.9%]. In a similar fashion 4i was converted to 21i (47%).

Preparation of Ethyl 2-oxopropanoate t-butylhydrazone (23). To a solution of ethyl glyoxalate t-butylhydrazone (22, prepared in situ) (0.860 g, 5.0 mmol) in THF (20 ml) at -78° was added n-butyl lithium (1 eq, 5.0 mmol). After 10 min. the solution was removed from the bath. After

10 further min. the solution was cooled to -78°, and methyl iodide (0.6 ml, 6.0 mmol) added, and the solution slowly allowed to warm to room temperature. The THF was removed, the solution dissolved in diethyl ether (50 ml), washed with water (3 x 40 ml), dried (sodium sulphate), filtered and concentrated. The product was bulb to bulb distilled using a Kugelrohr apparatus giving ethyl 2-oxopropanoate t-butylhydrazone (23) (0.566 g, 59%) as a mixture of isomers (E:Z - 25:75); b.p. 150° at 16 mmHg; ν_{max} ($CHCl_3$) 2980 m, 2940 m, 2910 w, 2875 w, 1690 m, 1535 m, 1368 m, 1328 m, and 1053 s, cm^{-1}; δH 1.16, 1.20 (9H, 2 x s, t-Bu), 1.19 (3H, t, J 7Hz, OCH_2CH_3) 1.85, 1.97 (3H, 2 x s, 3-CH_3), 4.05 (1H, br, NH), and 4.19 (2H, q, J 7Hz, O-CH_2); m/e (NH$_3$, C.I.) 187 (MH^+, 100%), 186 (M^+, 1%), 171 (6%), 130 (1%), 57 (30), and 56 (17); m/e (E.I.) 186 (M^+, 21%), 171 (71), 130 (11), 115 (21), 97 (28), 72 (15), 57 (100), and 56 (49).

Preparation of Methyl 2-oxopentanoate t-butylhydrazone (24). To a solution of butanal t-butylhydrazone(4e) (0.71 g, 5.0 mmol) in THF (20 ml) at 0°, was added n-butyl lithium (5.0 mmol). After 10 min. the reaction was cooled to -78°,and stirred for a further 10 min., when methyl chloroformate (5.0 mmol) was added. After 50 min. aqueous acetic acid (2M, 5 ml) was added, and the reaction warmed to room temperature. The THF was removed by concentration, diethyl ether added, the solution washed with saturated sodium carbonate solution (3 x 30 ml), dried (Na_2SO_4), filtered, and concentrated to yield a crude residue (0.709 g). Purification of a sample (97 mg) by p.l.c. [eluant dichloromethane] gave the title compound (24) (49 mg, 36%), t.l.c. [dichloromethane] Rf 0.4; ν_{max} ($CHCl_3$) 3270 br m, (N-H), 3035 w, 2970 s, 2940 m, 2879 m, 1743 s (C=O), 1456 m, 1438 m, 1368 m, 1241 m, and 1153 m cm^{-1}; δH 0.91 (3H, t, J 6Hz, 4-CH_3), 1.19 (9H, s, t-Bu), 1.20-1.26 (2H, br, 3-CH_2), 1.91 (2H, t, J 7Hz, 2-CH_2), and 3.70 (3H, s, OCH_3); m/e (NH$_3$, C.I.) 200 (M^+, 100%), 184 (67), 169 (26), and 57 (23); m/e (E.I.) 200 (M^+, 11%), 185 (5%), 57 (100), 56 (31) and 41 (38).

† In Schemes 5,6 the E/Z ratios were established by Nuclear Overhauser enhancement methods and subsequently by thermal equilibration of the isolated Z-isomers to their more stable E-forms.

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