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APPLICATIONS OF THE THERMAL ENE REACTION OF ALDEHYDE t-BUTYL- AND PHENYL- HYDRAZONES

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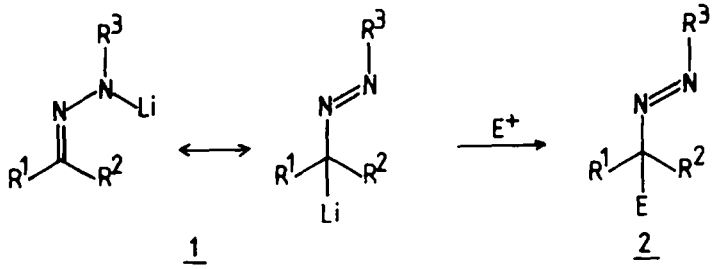
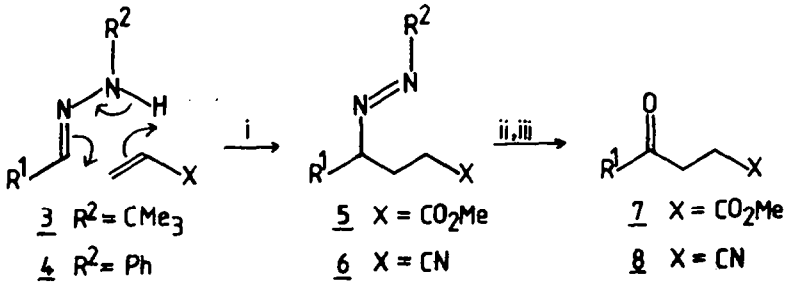
Abstract The Thermal Ene reaction of aldehyde t-butyl- and phenyl- hydrazones with enophiles gave C-trapped azo-adducts which can be diverted into synthetically useful γ-keto-esters, γ-keto-nitriles, γ-alkyl-2-pyrrolidones, and γ-amino-esters.

Recently we have described the use of azo anions in synthesis.[1,2,3] These anions derived from t-butyl, trityl- or diphenyl-4-pyridylmethyl-hydrazones 1 gave C-trapped azo products 2 when alkyl halides, aldehydes, ketones, or crotonates were chosen as the quenching electrophile (Scheme 1). However when methyl acrylate or acrylonitrile was the electrophile, negliable yields of C-trapped azo products 2 resulted. As an alternative to the anionic method, we have developed[3] a thermal ene reaction of aldehyde t-butyl-(3) and phenyl-(4) hydrazones[4] with these reagents as enophiles to produce the azo esters (5) and azo nitriles (6). These products (5), (6) have been converted into γ-keto-esters, γ-keto-nitriles, γ-alkyl-2-pyrrolidones, and γ-amino-esters. Herein we describe experimental details of these procedures.



Scheme 1

Initially the t-butylhydrazones of aliphatic aldehydes 3 were heated with methyl acrylate or acrylonitrile in toluene or xylene under reflux in an inert atmosphere to yield t-butylazo-esters 5 (R^2=CMe_3) and t-butylazo-nitriles 6 (R^2=CMe_3). These products could be isolated but usually they were tautomerised with trifluoroacetic acid and hydrolysed to γ-keto-esters 7 or γ-keto-nitriles 8 (Scheme 2, Table 1). Ketone t-butyl hydrazones were found to give negligible yields of γ-azo-esters with methyl acrylate under these conditions whilst benzaldehyde t-butylhydrazone gave no isoable γ-azo-ester with methyl acrylate. Attempted thermal reactions of aliphatic aldehyde t-butylhydrazones 3 with methyl crotonate, acrylic acid, methyl vinyl ketone, or methyl β,β-dimethylacrylate were also found to be unsuccessful.



Reagents: (i) Toluene or xylene, reflux, 24h, argon;
(ii) TFA, 20°, 80-300 min, argon;
(iii) $(CO_2H)_2$, H_2O, Et_2O, 20°, 5-16h., argon.

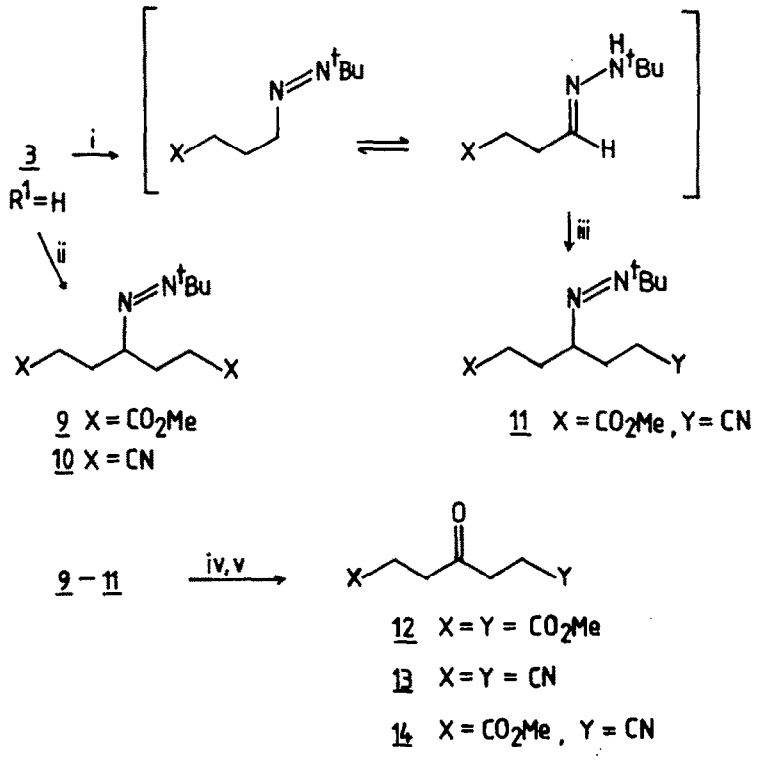
Scheme 2

Hydrazone 3	Product (%) from 3
R^1	
Me	7 80[a]
i-Pr	7 77[b]; 8 20[b]
n-Bu	6 58[b]; 7 75[b]; 8 55[b]
n-C_7H_{15}	7 90[b]; 8 75[b]

a) reaction in toluene
b) reaction in xylene

Table 1

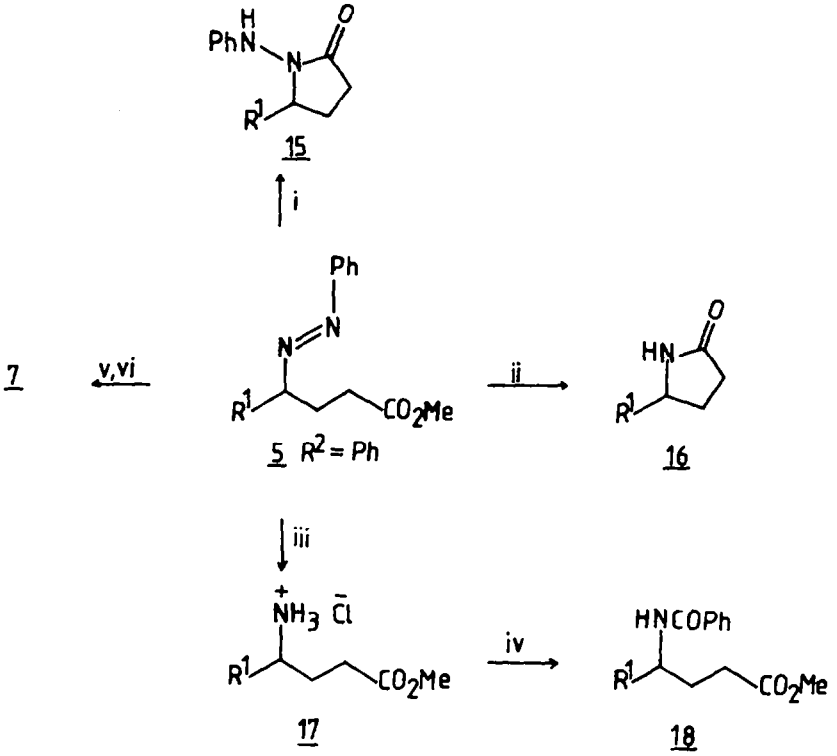
Formaldehyde t-butylhydrazone 3 (R^1=H) was found to be effective in these reactions. Thus upon heating at 100°C in xylene in the presence of 1.2 equivalents of methyl acrylate or acrylonitrile, 3 (R^1=H) gave azo ester 5 (R^1=H) (54%) or azo nitrile 6 (R^1=H) (71%) along with some minor amounts of double ene adducts 9 and 10. If an excess of the enophile was employed, then the double ene adducts 9 (52%) and 10 (80%) were isolated as the major products. Thermolysis of the initial azo-ester 5 (R^1=H) or azo-nitrile 6 (R^1=H) in the presence of acrylonitrile or methyl acrylate respectively gave the mixed adduct 11 (52% from 3 (R^1=H) via 6). Presumably the tautomerisation of the azo to hydrazone form of 5 (R^1=H) or 6 (R^1=H) occured under the reaction conditions. The azo product 9, 10, and 11 could be simply tautomerised and hydrolysed as before to yield the ketonic products 12 (77%), 13 (54%) and 14 (78%) respectively (Scheme 3).



Reagents: (i) ⟩X (1.2 equiv.), xylene, reflux, 15-20h., N_2;
(ii) ⟩X (2.5 equiv.), xylene, reflux, 50-70h., N_2;
(iii) ⟩Y (1.2 equiv.), xylene, reflux, 50-70h., N_2;
(iv) TFA, 20°, 80-300 min., argon;
(v) $(CO_2H)_2$, H_2O, Et_2O, 5-16h., 20°, argon.

Scheme 3

When aliphatic phenylhydrazones 4 were used for the thermal ene reaction with methyl acrylate[4], phenylazo esters 5 (R^2=Ph) were produced in moderate yields (56-60%). These adducts 5 (R^2=Ph) could be reductively cleaved to amines via azo cleavage, whereas the corresponding t-butyl azo adducts 5 (R^2=CMe_3) could not. Thus 5 (R^2=Ph) were reduced under mild conditions (Zn, HOAc, 60°, 1.5h.) to hydrazo-esters which upon work up, cyclised to 5-alkyl-1-(phenylamino)-2-pyrollidones 15 (45-52% from 4). Under more forcing conditions [Pd/C, H_2 (1 atm.), 50°, 12-24h.], 5 (R^2=Ph) gave 5-alkyl-2-pyrollidones 16 (45-51% from 4) arising from reductive cleavage of the azo function. With Adam's catalyst[5] [PtO_2, H_2 (1 atm), 20°, 24h.] in methanolic hydrogen chloride, the azo adduct 5 (R^2=Ph) gave the hydrochloride salts of γ-amino-esters 17[6] which were isolated as their N-benzoylderivatives 18. The phenylazo adducts 5 (R^2=Ph) could, like their corresponding t-butylazo derivatives 5 (R^2=CMe_3), be tautomerised and hydrolysed to γ-keto-esters 7 (41-52% from 4). (Scheme 4, Table 2).



Reagents: (i) Zn, HOAC, 60°, 1.5h.; (ii) Pd/C, H_2 (1 atm.), 50° 12-24h.; (iii) PtO_2, H_2 (1 atm.), 20°, 24h., MeOH-HCl; (iv) C_5H_5N, PhCOCl; (v) TFA, 20°, 5h., (vi) $(CO_2H)_2$, H_2O, Et_2O, 20°, 12h.

Scheme 4

Hydrazone 4	Product (%) from 4				
R^1	5(R^2=Ph)	7	15	16	18
H	60	-	48	51	33
Me	56	41	45	48	34
Et	57	44	45	46	34
i-Pr	56	52	52	45	38

Table 2

In summary we have shown that the thermal ene reaction of t-butylhydrazones 3 with enophilic reagents offers a useful method for the synthesis of γ-keto-esters and γ-keto-nitriles. A similar sequence applied to phenylhydrazones 4 gave phenylazo esters which allow reductive azo bond cleavage and thus offer an operational equivalent to an α-amino-carbanion. The t-butylhydrazones 3 give superior yields of the azo-esters 5 than the phenylhydrazones 4 presumably as the competing N - additon pathway with methyl acrylate is more sterically hindered.

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GENERAL EXPERIMENTAL

Standard laboratory practice as previously described[7] was observed. All ^{1}H N.M.R. spectra were recorded at 300MHz upon a Bruker WH 300 N.M.R. 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 N.M.R. spectra were recorded at 62.85MHz or 75.4MHz on either a Bruker AM 250 or Bruker WH 300 spectrometer respectively, using $CDCl_3$ as solvent, referenced to $CDCl_3$ = 77.00 p.p.m. unless otherwise stated. Only selected I.R, ^{1}H, and ^{13}C N.M.R. signals are assigned. Accurate mass measurements were recorded from the electron impact (E.I.) mode only. The preparation of t-butylhydrazones 3 is described elsewhere[6] whilst phenylhydrazones 4 were prepared by literature procedures[5]. 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.

General procedure for the preparation of t-Butylazo-esters 5 (R^2= CMe_3) and t-Butylazo-nitriles 6 (R^2= CMe_3) from aldehyde t-butylhydrazones (R^1= H).

The procedure for the preparation of 4-(t-butylazo)octanitrile 6 (R^1= n-Bu, R^2= CMe_3) from pentanal t-butylhydrazone 3 (R^1= n-Bu) and acrylonitrile is typical of all azo-ester 5 (R^2= CMe_3) or azo-nitriles 6 (R^2= CMe_3) preparations.

A solution of 3 (R^1= n-Bu) (5.0 mmol) and acrylonitrile (15.0 mmol) was heated in xylene or toluene (10ml) under reflux in an inert atmosphere for 24h. The solvent and excess acrylonitrile were removed by concentration to give the crude azo product. Purification by column chromatography [50g silica gel, diethylether: petroleum (1:9 - 1:4) as eluant] gave a crude residue (736 mg) from which a sample (183 mg) was purified by p.l.c. [2 x 20 x 20 x 0.1 cm silica plates, diethyl ether: light petroleum (1:3)] to yield 4-(t-butylazo)octanitrile 6 (R^1= n-Bu, R^2= CMe_3) (151mg, 58%) b.p. 98° at 0.65 mm Hg; t.l.c. [SiO_2, diethylether: petroleum (1:3)] Rf 0.3; νmax (film) 2965 s, 2935 s, 2875 m, 2255 w, (C≡N), 1468 m, 1454 m, 1427 m, 1365 m, and 1211 m cm^{-1}, δH 0.87 (3H, t, J 8Hz, $MeCH_2$), 1.19 (9H, s, CMe_3), 1.13-1.30 (4H, m), 1.55-1.66, 1.72-1.84, 1.93-2.04, 2.13-2.25 (6H, 4 x m), and 3.29-3.37 (1H, m, C(4)-H), δC 13.84 (q, CH_2Me), 13.92, 22.39, 27.72, 28.98, 32.60 (5 x t, CH_2), 26.89 (q, CMe_3), 67.35 (s, CMe_3), 75.12 (d, C(4)), and 119.35 (s, C≡N); m/e (NH_3 C.I.) 210 MH^+, 100%); [Found: C, 69.1%; H, 11.1%; N, 20.3%. $C_{12}H_{23}N_3$ C, 68.9%; H, 11.1%, N, 20.1%.]

General procedure for the preparation of γ-keto-esters 7 and γ-keto-nitriles 8 from t-butylhydrazones 3

The procedure for the preparation of methyl 4-oxopentanoate 7 (R^1=Me) is typical of all γ-keto-ester 7 and γ-keto-nitrile 8 preparations.

3 (R^1=Me) (4.5 mmol) was reacted with methyl acrylate as before to give a crude t-butylazo ester 5 (R^1=Me) which was dissolved in trifluoroacetic acid (2ml) under nitrogen and stirred for 5h. The acid was evaporated and the residue dissolved in oxalic acid (2g), water (20ml) and diethyl ether (5ml) and the solution stirred for 5-16h. The aqueous phase was separated, extracted with diethylether (2 x 50ml), the organic layers combined, dried, filtered, and evaporated. Purification by column chromagraphy [50g silica, eluant diethylether: dichloromethane (1:24)] and p.l.c. [eluant diethylether: dichloromethane (3:197)] gave methyl 4-oxopentanoate 7 (R^1=Me) (468 mg, 80%); b.p. 126° at 15 mmHg; t.l.c. [diethylether: dichloromethane (1:39)] Rf 0.2; νmax (film) 2960 m, 1738 s, (C=O), ester), 1716 s (C=O, ketone), 1440 m, 1410 m, 1362 m, 1318 m, 1268 m, 1214 m, and 1162 s cm^{-1}; δH 2.21 (3H, s, MeCO), 2.57-2.62, 2.75-2.80 (4H, 2 x m, CH_2CH_2), 3.69 (3H, s, OMe); δC 27.66 (t, CH_2), 29.66 (q, MeCO), 37.83 (t, CH_2), 51.59 (q, OMe), 172.98 (s, CO_2), and 206.30 (s, CO); m/e (E.I.) 130 (M^+, 30%), 115 (23), 99 (29), and 43 (100); [Found: C, 55.2%; H, 7.6%. $C_6H_{10}O_3$ requires C, 55.4%; H, 7.7%.].

Similarly prepared from 3 (R^1= n-Bu) (5.0 mmol.) and acrylonitrile, followed by tautomorisation and hydrolysis, 4-oxooctanitrile 8 (R^1= n-Bu) (55%); b.p. 119° at 0.8 mmHg; t.l.c. (dichloromethane) Rf 0.3; νmax. (film) 2960 s, 2940 s, 2880 m, 2250 m (C≡N), 1715 s (C=O), 1460 m, 1414 m, 1379 m, 1127 m, and 1076 m, cm^{-1}; δH 0.88 (3H, t, J 7H_z, CH_3), 1.29 (2H, ca sextet, J 8Hz, 7-CH_2), 1.56 (2H, ca pentet, J 8Hz, 6-CH_2), 2.43 (2H, t, J 8Hz, 5-CH_2), and 2.53-2.58, 2.75-2.80 (4H, 2 x m, 2,3-CH_2); δC 11.30 (t, CH_2CN), 13.66 (q, CH_3), 22.16, 25.70, 37.59, 42.13 (4 x t, 4 x CH_2), 118.94 (s, CN), and 206.15 (s, CO); m/e (NH_3 C.I.) 157 (MNH_4^+, 100%), 140 (MH^+, 2), 85 (9), and 69 (15); [Found C, 69.0%; H, 9.2%; N, 9.9%. $C_8H_{13}NO$ requires C, 69.0%; H, 9.4%; N, 10.1%].

General procedure for the preparation of t-Butylazo-esters 5(R^1=H, R^2= CMe_3 and t-butylazo-nitriles 6 (R^1=H, R^2= CMe_3) from formaldehyde t-butylhydrazones 3 (R^1=H).

3 (R^1=H) (1.0g, 10.0 mmol) and methyl acrylate (or acrylonitrile) (12.0 mmol) were dissolved in xylene (10 ml) and heated at 100° for 15h. Evaporation and purification by column chromatography on flash silica [(40g), hexane: ethyl acetate (19:1) as eluant] gave 5 (R^1=H) (1.0g, 54%) or 6 (R^1=H) (1.1g, 71%) respectively as oils, along with some double adducts 9 or 10 (<5%). For 5 (R^1=H) νmax. (thin film) 2970 s, 2870 s, 1735 s (CO_2), 1438 s, 1360 s, 1315 m, 1220 br, 1165

br, and 1002 m cm^{-1}; δH 1.07 (9H, s, t-Bu), 1.95-2.05 (2H, m, 3-H), 2.29 (2H, t, J 7.5Hz, 2-H), 3.56 (3H, s, OMe), 3.66 (2H, t, J 7Hz, 4-H); δC 22.97(t), 26.68(q), 31.56(t), 51.35(q), 66.88(s), 67.54(t), 173.22(s); m/e (NH_3 C.I.) 187 (MH^+, 100%). For 6 (R^1=H) νmax. (thin film) 2970 s, 2930 m, 2870 m, 2250 m, 1472 m, 1455 m, 1428 m, 1360 s, 1228 m, 1210 m cm^{-1}; δH 1.11 (9H, s, t-Bu), 2.03-2.12 (2H, m, 3-H), 2.38 (2H, t, J 7Hz, 2-H), 3.77 (3H, t, J 6.5Hz, 4-H); δC 15.04(t), 23.71(t), 26.69(q), 66.20(t), 67.43(s), 119.11(s); m/e (NH_3 C.I.) 154 (MH^+, 100%).

General procedure for the preparation of double adducts 9 and 10

3 (R^1=H) (1.0g, 10.0 mmol) was refluxed with methyl acrylate (or acrylonitrile) (10.0 mmol.) in xylene (10ml) under an inert atmosphere for 12-15h. Further enophile (20 mmol) was added and reflux was continued for 40-50h. Evaporation and chromatography on flash silica gel [(50g), dichloromethane as eluant] gave 9 (1.4g, 52%) and 10 (1.7g, 80%) respectively as oils, along with some mono adducts 5 (R^1=H) or 6 (R^1=H) (<5%). For 9: νmax. (thin film) 2975 m, 2935 m, 1740 s (CO_2), 1438 m, 1363 m, 1250 m, 1200 m, 1175 s, 1100 w, and 1018 w cm^{-1}; δH 1.14(9H, s, t-Bu), 1.91-2.17(8H, m, $CH_2CH_2CO_2Me$), 3.20-3.24(1H, m, CHN_2), 3.60(6H, s, OMe); δC 26.77(q), 28.08 (t), 30.21(t), 51.34(q), 67.12(s), 74.97(d), 173.18(s); m/e (NH_3 C.I.) 273(MH^+, 100%). For 10: νmax. (thin film) 2975 s, 2930 s, 2250 s (C≡N), 1475 m, 1450 s, 1426 s, 1390 w, 1364 s, 1230 m, 1210 m, and 1093 w cm^{-1}; δH 1.20(9H, s, t-Bu), 1.93-2.31(8H, m, $CH_2CH_2CO_2Me$), 3.44-3.51(1H, m, CHN_2); δC 13.72(t), 26.68(q), 28.53(t), 68.20(s), 72.94(d), 118.73(s); m/e (NH_3 C.I.) 207 (MH^+, 100%).

Preparation of mixed adduct 11

6 (1.0g, 6.5 mmol) and methyl acrylate (0.86g, 10.0 mmol) were dissolved in xylene (10ml) and the mixture refluxed for 60-70h. Evaporation and purification by chromatography on flash silica [(45g), dichloromethane as eluant] gave 11 (1.13g, 73%) as a gummy mass, νmax. (thin film) 2970 m, 2935 m, 2250 m (CN), 1740 s (CO_2), 1475 w, 1440 m, 1365 m, 1330 w, 1250 w, 1200 m, 1170 m, and 1095 w cm^{-1}; δH 1.16(9H, s, t-Bu), 1.94-2.23(8H, m), 3.32-3.35(1H, br, CHN_2), 3.62(3H, s, OMe); δC 13.95(t), 26.93(q), 27.88(t), 28.86(t), 30.08(t), 51.59(q), 67.77(s), 74.05(d), 119.06(s), 173.06(s); m/e (NH_3 C.I.) 240 (MH^+, 100%).

General procedure for the preparation of dimethyl 4-oxopimelate 12, 3-oxopentan-1,5-dinitrile 13, and methyl 6-cyano-4-oxohexanoate 14

The procedure for the preparation of 12 is typical for the preparation of 13 or 14.

9 (0.655g, 2.4 mmol) was dissolved in dry benzene (5ml) and TFA (0.5ml) and the mixture stirred under nitrogen for 5h. Evaporation gave a residue which was dissolved in diethylether (3ml), water (10ml) and oxalic acid dihydrate (315 mg) and stirred for 20h. under nitrogen. The aqueous layer was extracted with diethylether (3 x 20ml), the organic layers combined, dried, filtered, and evaporated. Purification by column chromatography on flash silica [(20g), dichloromethane as eluant] gave 12 (370 mg, 77%), m.p. 55°C (Lit.,[9] m.p. 53°); νmax. (nujol) 1745 s (CO_2), 1705 s (CO), 1418 s, 1332 s, 1205 s, 1105 s, 990 m, and 918 s cm^{-1}; δH 2.58(4H, t, J 7Hz), 2.75(4H, t, J 7Hz), 3.63(6H, s, OMe); δC 27.68(t), 37.04(t), 51.71(q), 173.01(s), 206.77(s); m/e (NH_3 C.I.) 220 (MNH_4^+, 18%), 203 (MH^+, 33), 118 (33), and 171 (100).

Similarly prepared by tautomerisation and hydrolysis:- 13[10] [0.62g, 54% from 10 (8.25 mmol)]; t.l.c. [SiO_2, dichloromethane Rf 0.1] m.p. 37°; νmax. (nujol) 2250 s (CN) 1710 s (CO), 1425 s, 1410 s, 1400 s, 1350 s, 1335 m, 1258 m, 1210 m, 1100 s, and 1015 s cm^{-1}; δH 2.60(4H, t, J 7Hz), 2.85(4H, t, J 7Hz); δC 11.19(t), 37.30(t), 118.63(s), 202.03(s); m/e (NH_3 C.I.) 154 (MNH_4^+, 100%), 137 (MH^+, 1).

14 [0.395g, 78% from 11 (3.0 mmol)]; b.p.230-5°C at 30mmHg; νmax. (thin film) 2960 m, 2255 m (CN), 1740 s (CO_2), 1722 s (CO), 1440 m, 1418 m, 1368 m, 1315 w, 1265 m, 1200 m, 1180 m, 1115 m, and 1105 s cm^{-1}; δH 2.48-2.56(4H, 2 x t, J 7,6Hz), 2.67(2H, t, J 6Hz), 2.80(2H, t, J 7Hz), 3.57(3H, s, OMe); δC 11.19(t), 27.58(t), 36.56(t), 37.68(t), 51.73(q), 118.78(s), 172.69(s), 204.35(s); m/e (NH_3 D.C.I.) 187 (MNH_4^+, 100%), 170 (MH^+, 5); [Found: C, 56.6%; H, 6.6%; N, 8.1%. $C_8H_{11}NO_5$ requires C, 56.8%; H, 6.5%; N, 8.3%].

General procedure for the preparation of γ-Phenylazo-esters 5 (R^2=Ph)

The following procedure for the preparation of 5 (R^1 = i-Pr, R^2=Ph) is typical.

4 (R^1= i-Pr) (1.62g, 10.0 mmol) and methyl acrylate (1.72g, 20.0 mmol) were dissolved in xylene (20ml) and the solution refluxed for 20-24h. under nitrogen. Evaporation and chromatography on flash silica [(60g), hexane: ethyl acetate (49:1) as eluant] gave 5 (R^1= i-Pr, R^2=Ph)* (1.40g, 56%) as a single isomer*; yellow viscous oil; νmax. (thin film) 1743 s (CO_2), 1594 w, 1521 w, 1457 w, 1440 w, 1392 w, 1372 w, 1260 m, 1200 m, 1176 m, 1075 w, and 1024 w cm^{-1}; δH 0.96(3H, d, J 7Hz $CHMe_2$), 1.03(3H, d, J 7Hz $CHMe_2$), 2.13-2.39 (5H, m), 3.28-3.34(1H, m, CHN_2), 3.61(3H, s, OMe), 7.35-7.75(5H, m, Ph-H); δC 19.07(q), 19.27(q), 25.71(t), 30.86(t), 31.86(d), 51.44(q), 82.64(d), 122.23(d), 128.89(d), 130.30(d), 151.90(s), 173.60(s); m/e (E.I.) 249($M+1^+$, 0.2%), 143(41), and 77(100).

General procedure for the preparation of Pyrollidones 15

The following procedure for the preparation of 15 (R^1= i-Pr) is typical.

5 (R^1= i-Pr, R^2=Ph) (0.30g, 1.21 mmol) was dissolved in 50% aqueous ethanol (15ml) and acetic acid (1.2ml) at 60°. Zinc powder (1.0g) was added in portions over 1.5h.. The ethanol was evaporated, the residue neutralized with saturated $NaHCO_3$ solution and extracted into dichloromethane (2 x 25ml). The organic layers were combined, washed with water (20ml), dried, filtered and evaporated. Purification by p.l.c. [SiO_2, ethyl acetate: hexane (6:4) as eluant] gave 5-isopropyl-1-(phenylamino)-2-pyrrolidone 15 (244 mg, 92%) as a white solid m.p. 85°; νmax. (nujol mull) 3220 s (NH), 3100 w, 3020 m, 1690 s (NHCO), 1600 s, 1490 m, 1408 m, 1388 m, 1302 m, 1263 m, and 1082 m cm^{-1}; δH 0.85(3H, d, J 7Hz, $CHMe_2$), 0.93(3H, d, J 7Hz, $CHMe_2$), 1.81-2.33(3H, m), 2.35-2.56(2H, m), 3.76-3.88(1H, m, CHN), 6.06(1H, br, NH), 6.66-7.30(5H, m, Ph-H); δC 15.16(q), 16.92(q), 18.27(t), 28.27(t), 28.39(d), 62.45(d), 113.55(d), 120.95(d), 129.13(d), 146.07(s), 174.10(s); m/e (E.I.) 218 (M^+, 55%), 175(62), 92(100); [Found: C, 71.9%; H, 8.0%; N, 12.8%. $C_{13}H_{18}N_2O$ requires C, 71.6%; H, 8.2%; N, 12.8%].

General procedure for the preparation of 5-alkyl-2-pyrrolidone 16

The following procedure for the preparation of 16 (R^1= i-Pr) is typical.

5 (R^1= i-Pr, R^2=Ph) (0.496g, 2.0 mmol) was dissolved in methanol (10ml). 10% palladium on carbon (75mg) was added and the mixture hydrogenated at 50° and 1 atmosphere pressure for 18-20h.

The catalyst was filtered off, washed with methanol (2 x 10ml), the organic layers combined and evaporated. Purification by p.l.c. [SiO_2, ethyl acetate: hexane (7:3)] gave 5-isopropyl-2-pyrrolidinone 16 (R^1= i-Pr) (198 mg, 78%), as a while solid m.p. 71°C, νmax. (nujol mull) 3195 br (N-H), 1695 s (NHCO), 1425 w, 1390 m, 1293 m, 1270 m, and 1083 w cm^{-1}; δH 0.90 (3H, d, J 7Hz $CHMe_2$), 0.94(3H, d, J 7Hz, $CHMe_2$), 1.58-1.83(2H, m), 2.1-2.2(1H, m), 2.30-2.35(2H, m), 3.34-3.41(1H, m, CHN), 6.45(1H, NH, br s); δC 18.07(q), 18.71(q), 24.65(t), 30.59(t), 33.50(d), 60.62(d), 178.69(s); m/e (NH_3 C.I.) 128 (MH^+, 100%), 84(15); [Found: C, 66.5%; H, 10.0%; N, 10.9%. $C_7H_{13}NO$ requires C, 66.1%; H, 10.2%; N, 11.0%].

General procedure for the preparation of γ-amino-esters 18

The following procedure for the preparation of 18 (R^1= i-Pr) is typical.

5 (R^1= i-Pr, R^2=Ph) (375 mg, 1.5 mmol) was dissolved in dry methanolic hydrogen chloride (1M, 7ml). Adam's catalyst (75 mg) was added and the mixture hydrogenated at 1 atm. pressure at 20° for 15h. The catalyst was filtered off, washed with methanol (2 x 10ml), the organic layers combined and evaporated to yield the amine salt 17 (R^1= i-Pr) and cyclohexylamine. The mixture was dissolved in dichloromethane (3ml); benzoyl chloride (0.63g) and pyridine (1ml) and stirred overnight at 20°. The solution was acidified with aqueous 2M hydrochloric acid, the aqueous layer separated and extracted with dichloromethane (2 x 25ml). The organic layers were combined, dried, filtered and evaporated. Purification of the residue by p.l.c. [SiO_2, chloroform: ethyl acetate (9:1) as eluant] gave 18 (R^1= i-Pr) (270 mg, 68%) as a white solid m.p. 75°; νmax. (nujol mull) 3320 s (NH), 1738 s (CO_2), 1633 s (NHCO), 1603 m, 1580 m, 1543 s, 1494 m, 1440 m, 1318 m, 1175 m, and 1080 w cm^{-1}; δH 0.98(3H, d, J 7Hz, $CHMe_2$), 0.99(3H, d, J 7Hz $CHMe_2$), 1.73-2.02(3H, m), 2.33-2.50(2H, m), 3.57(3H, s, OMe), 4.01-4.10(1H, m, CHN), 6.0(1H, br d, J 9Hz, NH), 7.41-7.80(5H, m, Ph-H); δC 18.15(q), 18.98(q), 26.86(t), 31.12(t), 32.47(d), 51.52(q), 54.62(d), 126.75(d), 128.43(d), 131.25(d), 134.60(s), 167.21(s), 174.42(s); m/e (E.I.) 263(M^+, 0.5%), 220(15), 105(100); [Found: C, 68.8%; H, 7.9%; N, 5.3%. $C_{13}H_{21}NO_3$ requires C, 68.4%; H, 8.0%; N, 5.3%].

General procedure for the preparation of γ-keto-esters 7 from γ-phenylazo-esters 5 (R^2=Ph)

The following procedure for the preparation of 7 (R^1=Me) is typical.

5 (R^1=Me, R^2=Ph) (0.44g, 2.0 mmol) was dissolved in TFA (2ml) and stirred under nitrogen for 5-6h. The solvent was evaporated, the residue dissolved in water (10ml), diethylether (5ml) and oxalic acid (0.40g) and stirred for 12h. The aqueous phase was separated, extracted with diethylether (2 x 20ml), the organic layers combined, dried, filtered and evaporated. Distillation gave 7 (R^1=Me) (185 mg, 71%) b.p. 126° at 15 mmHg, t.l.c., n.m.r. as before.

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