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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 20.[1] DECARBOXYLATION OF α-IMINO ACIDS. MECHANISM AND APPLICATIONS TO THIOAMIDE SYNTHESIS

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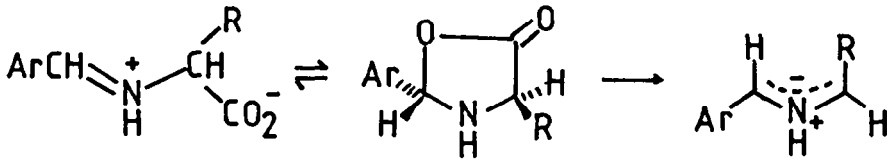
α-Imino acids, prepared from α-keto acids and primary amines, undergo facile decarboxylation to the corresponding imines on heating at ≤80°C in benzene or methylene chloride. Decarboxylation proceeds via a 1,2-ylide which can be trapped by sulphur to give the corresponding secondary thioamides in good yield. 1,2-Ylides from secondary amines and α-keto acids can be generated in situ and trapped with sulphur to give tertiary thioamides in excellent yield.

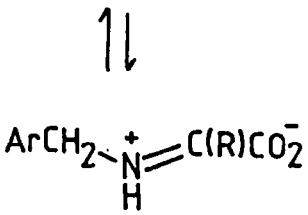
Pyridoxal enzymes are responsible for a wide range of biochemical transformations of α-amino acids. We have recently provided evidence that many of these processes in vitro, in which the carboxylic acid group is either retained[2] or lost[3], involve 1,3-dipoles. Thus we have shown that decarboxylative transamination[4] proceeds via cyclisation of the initial imine (1) to an oxazolidine-5-one (2) followed by cycloreversion with loss of carbon dioxide to generate an anti-azomethine ylide (3) usually stereospecifically or with high stereoselectivity.[1,5,6]

The related biochemical transamination processes effected by pyridoxal enzymes involve initial prototropy of the imine (1)⟶(4).[7] The isomeric imine (4) is an imine of an α-keto acid. Non-oxidative enzyme catalysed decarboxylation of α-keto acids to aldehydes involves adduct formation with thiamine pyrophosphate via C-C bond formation and it is generally considered that this is essential because α-keto acids lack a suitable electron sink to stabilise negative charge development during decarboxylation.[8,9] However, it is well known that pyridine-2-carboxylic acid (5a) and the related betaines (5b) undergo ready decarboxylation to the ylides (6a) and (6b) respectively, which can be trapped by aldehydes and other electrophiles (Hammick reaction).[10] Furthermore, the ready deprotonation of azolium cations (7a) at C(2) to give (8)[11] is the basis of the biochemistry of thiamine pyrophosphate[8,9,12] and important synthetic methodology for C-C bond formation.[13] Ylide (8) is also readily generated by decarboxylation of the corresponding azolium 2-carboxylates (7b).[14] Thus the moiety (9) possesses intrinsic stabilising features when part of an aromatic ring in which R is a heteroatom or an sp^2 carbon centre. The enhanced stability is usually attributed to carbene resonance (9)⟷(10), but it is unclear if the presence of the ring provides additional stability. Prior to our work[15] acyclic examples of 1,2-ylides (9) had not been reported although our STO-3G calculations indicate that acyclic cases of (9) with certain substituents should be more stable than (6a), with

stabilisation of (9) increasing in the order R=NO_2 < Ph < p-$MeOC_6H_4$ < p-$O_2NC_6H_4$ < SMe.[16] The existence of acyclic ylides of type (9) was foreshadowed in earlier experiments on the decarboxylation of certain α-keto acids (pyruvic and benzoylformic), in the presence of catalytic amounts of primary amines, carried out by Boklund[17] and by Langenbeck.[18] We have studied several series of imines as potential precursors of acyclic ylides (9) and these are now considered in turn.



(1) (2) (3)



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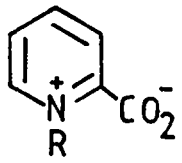
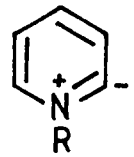
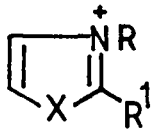


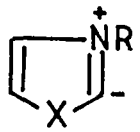
(5) a. R=H
b. R=alkyl



(6) a. R=H
b. R=alkyl

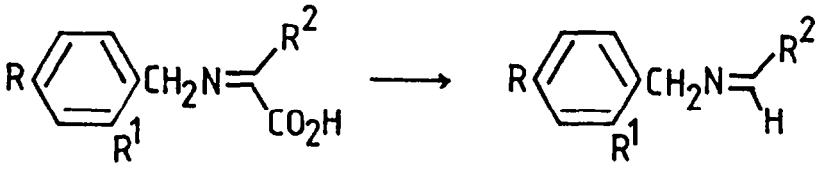


(7) a. R^1= H
b. R=H, R^1= CO_2^-



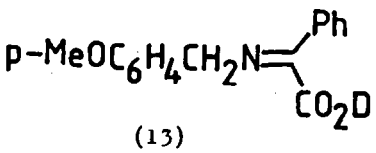
(8)

(9) (10)



(11) (12)

a. R=R^1=H, R^2=Ph
b. R=MeO, R^1=H, R^2=Ph
c. R=Me, R^1=H, R^2=Ph
d. R=NO_2, R^1=H, R^2=Ph
e. R=H, R^1=OMe, R^2 = 2-thienyl



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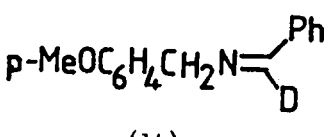
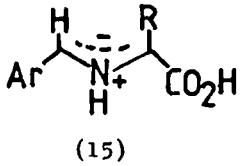


(14)



(15)

Reactions of α-Keto Acids with Primary Amines

a. Benzylamines. A series of imines (11a-e) was prepared by stirring a mixture of α-keto acid and the appropriate benzylamine in methylene chloride at room temperature for 15 min. during which time the α-imino acid crystallised out in quantitative yield.

α-Imino acids (11a-e) are smoothly decarboxylated to (12a-e) on heating in boiling benzene for less than 30 min. Decarboxylation of the imino acids (11a-e) might proceed via prototropy, cyclisation and decarboxylation (4)→ (1)→ (2)→ (3), followed by subsequent prototropy (3)(Ar=CH_2Ar)→(12). This mechanism was ruled out since decarboxylation of the deuterated α-imino acid (13) in boiling methylene chloride for 4h afforded (14), in which the deuterium label was located solely on the imine carbon atom. The signal for the imine proton (CH=N) of (12b) at δ 8.2 was absent in (14) and mass spectrometry confirmed the regiospecific deuteration. Thus both (14) and (12b) exhibit the same ratio of peaks at m/z 121 and m/z 122. The peak at m/z 121 is due to p-$MeOC_6H_4CH_2^+$ (or more correctly the corresponding tropylium ion) and is the base peak in both spectra. Any isomerisation of the type (1)⇌(4) would be expected to proceed via the 1,3-dipole (15). However, when imine (12b) was heated in boiling methylene chloride in the presence of N-phenylmaleimide (NPM) (an excellent dipolarophile)[2] only the decarboxylation product (12b) was obtained and the NPM was recovered quantitatively. Decarboxylation can be achieved without isolation of the α-imino acid. Thus benzoylformic acid and benzylamine react (CH_2Cl_2, 40°C, 3h) to give a quantitative yield of (12a).

b. Aliphatic Amines. Aliphatic imino acids (16a) and (16b) were prepared in a similar manner to (11a-e) except that (16a) required a longer reaction time (14h) and (16b) was prepared in benzene as solvent. Decarboxylation of (16a) and (16b) to the corresponding imines (17a) and (17b) occurs rapidly (< 0.5h) in boiling benzene.

(16) (17)

a. R=cyclo-C_6H
b. R=Bu^n
c. R=p-MeO C_6H_4
d. R=Ph
e. R=p-$O_2NC_6H_4$
f. R=$NHCO_2Et$
g. R=NHCOPh
h. R= 

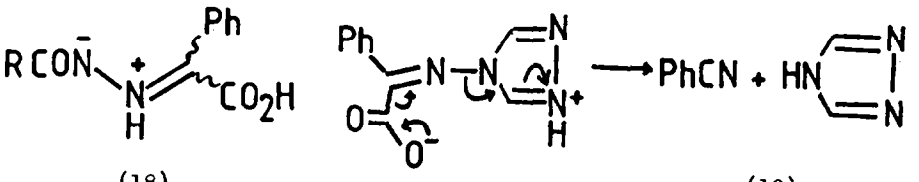
c. Arylamines. The para substituent on the benzene ring has the expected effect on rate of formation of α-imino acid in methylene chloride at room temperature. Monitoring by p.m.r. gave the following order and time for formation of the imino acids (16c-e): MeO (5min) > H (60min) > NO_2 (240min). When benzoylformic acid and p-arylamines are heated in boiling methylene chloride consecutive α-imino acid formation and decarboxylation occur furnishing (17c-e) in good yield with the rate again dependant, as expected, on the p-substituent of the arylamine: MeO (1.67dy) > H (5dy) > NO_2 (11dy).

Reactions of α-Keto Acids with Hydrazine Derivatives

The hydrazones (16f-h) were prepared by reacting benzoylformic acid with the appropriate hydrazine in methylene chloride at room temperature. The hydrazone derivatives undergo thermal decarboxylation more slowly than the corresponding aliphatic- and benzyl-imines. Thus (16f) requires heating at 80°C (benzene or

acetonitrile) for 2-3 dy to effect conversion to (17f), whilst decarboxylation of (16g) to give (17g) requires heating for ca.14h in benzene. When both of these reactions were repeated in the presence of N-methylmaleimide the products were exclusively (17f) and (17g) respectively showing 1,3-dipoles (18) were not being produced in these reactions. We have previously shown that azomethine imine formation by thermal 1,2-prototropy occurs in certain hydrazones.[19]

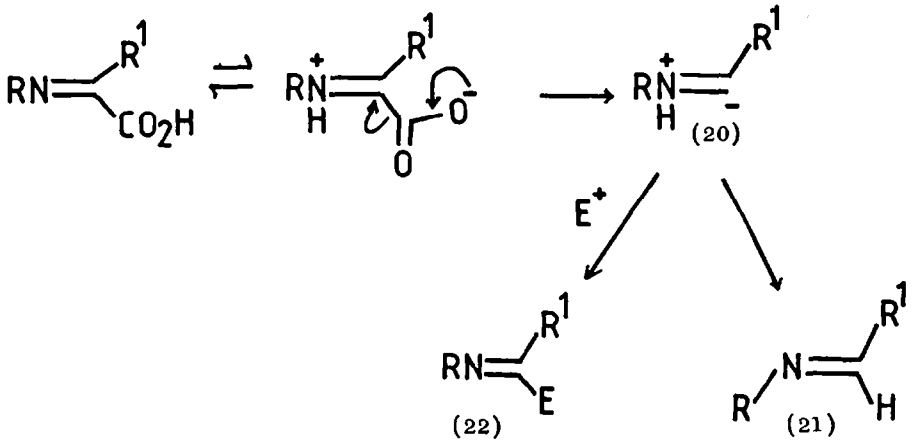
In contrast to (16f) and (16g), the hydrazone (16h) on heating in boiling benzene for 1h undergoes fragmentation to benzonitrile and 1,3,4-triazole (19).



(18) (19)

Mechanism and Capture of Intermediate Ylide with Sulphur

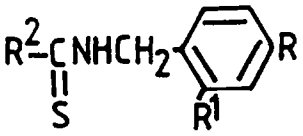
The deuterium labelling experiment and the failure of attempts to trap intermediate 1,3-dipoles with N-substituted maleimides points to a common mechanism for the decarboxylation of the imines of α-keto acids and primary amines and the hydrazones (16f) and (16g). By analogy with the Hammick reaction the mechanism is believed to be that outlined in the Scheme.



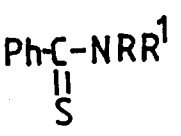
(20) (22) (21)

SCHEME

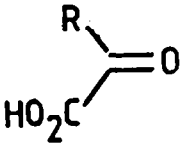
Attempts to trap the intermediate ylides (20) (Scheme) with aryl aldehydes were unsuccessful, although the reaction of the corresponding cyclic ylides (20) with appropriate electrophiles to give (22) appears to be quite general.[20] Transimination and competitive proton transfer (20)→(21) intervene in our examples. However, reaction of the α-imino acids (11a-e) and (16a-e) with a 10 molar excess of sulphur in boiling benzene for ca. 20min. afforded the corresponding thioamides (23a-e) and (24a-e) in 70-80% yield, together with some of the corresponding decarboxylation products (12a-e) and (17a-e) respectively. The thioamides can be prepared directly from benzoylformic acid and the primary amine by heating with excess sulphur in boiling benzene. This is the method of choice for (23f). Trapping of azolium ylides (8) with sulphur has been reported previously.[21]



(23) a. R=R^1=H,R^2=Ph
b. R=MeO,R^1=H,R^2=Ph
c. R=Me,R^1=H,R^2=Ph
d. R=NO$_2$,R^1=H,R^2=Ph
e. R=H,R^1=OMe,R^2=2-thienyl
f. R=H,R^1=OMe,R^2=Ph

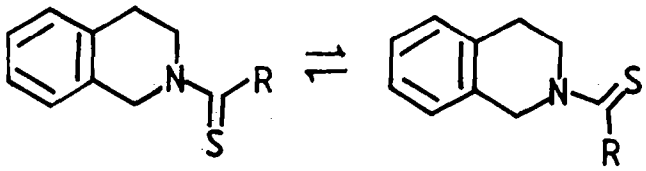


(24) a. R=cyclo-C$_6$H$_{11}$,R^1=H
b. R=Bu^n,R^1=H
c. R=p-MeOC$_6$H$_4$,R^1=H
d. R=Ph,R^1=H
e. R=p-O$_2$NC$_6$H$_4$,R^1=H

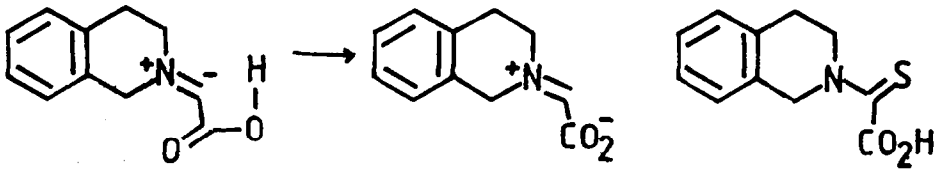


(25)

Reactions of α-Keto Acids with Secondary Amines and Sulphur. When a mixture of a secondary amine, α-keto acid (25) and sulphur (10mol excess) are heated in boiling benzene for ca. 15 min., the corresponding thioamides (Table 1) are obtained as mixtures of geometrical isomers, e.g. (26)⇌(27), arising from restricted rotation about the thioamide bond, in near quantitative yield. The reaction appears to be general for secondary amines and the yields are invariably substantially better than those obtained from primary amines (above) due to the absence of the competing 1,2-prototropy (20)→(21) (Scheme). The reaction rate depends, as expected, on the nucleophilicity of the amine (Table 1). Pyruvic acid reacts with 1,2,3,4-tetrahydroisoquinoline and sulphur to give the corresponding thioamide (26, R=Me) in good yield (Table 1). In contrast pyruvic acid, primary amines, and sulphur react to give complex mixtures of products. However, formation of (26, R=Me) shows the reaction functions even in cases where enamine formation might intervene. It is interesting that when α-keto malonic acid (25, R=CO$_2$H) reacts with 1,2,3,4-tetrahydroisoquinoline and sulphur, the product is (26, R=H), i.e. a double decarboxylation takes place. This suggests that either rapid intramolecular C-protonation of the initial ylide (29)→(30) occurs, possibly via hydrogen-bonded water, or that decarboxylation of the thioamide (31) is promoted by the ability of sulphur to stabilise an α-carbanion.



(26) (27) (28)



(29) (30) (31)

Table 1. Thioamides from the reaction of α-keto acids (25), secondary amines, and sulphur (benzene, 80°C).

α-Keto Acid (25) R	Secondary Amine	Reaction Time(min)	Product	Yield[a] (%)
H	1,2,3,4-tetrahydro-isoquinoline	15	26,R=H	80
CO_2H	"	15	26,R=H	80
Me	"	15	26,R=Me	75
cyclo-C_3H_5	"	15	26,R=cyclo-C_3H_5	100
Ph	"	15	26,R=Ph	100
p-$O_2NC_6H_4$	"	15	26,R=p-$O_2NC_6H_4$	80
PhCH=CH	"	15	26,R=PhCH=CH	80
2-furyl	"	15	26,R=2-furyl	90
2-thienyl	"	15	26,R=2-thienyl	100
Ph	pyrrolidine	10	28,X=CH_2	100
Ph	piperidine	45	28,X=$(CH_2)_2$	100
Ph	morpholine	45	28,X=CH_2O	100
Ph	thiazolidine	15	28,X=S	80
Ph	PhN(Me)H	360	24,R=Me,R^1=Ph	58[b]
Ph	Et_2NH	360	24,R=R^1=Et	80[b]

a. Isolated yield

b. Estimated by p.m.r. spectroscopy

Thioamides exhibit higher barriers to rotation about the C(S)-N bond than the corresponding rotation about the C(O)-N bond in amides,[22] and, as expected, the thioamides listed in the Table 1 show the presence of two isomeric forms. The isomer ratios for the thioamides derived from 1,2,3,4-tetrahydroisoquinoline are collected in Table 2.

The major isomer from the isomeric mixture of (26)⇌(27) (R=H) crystallised from a solution in 40-60°C petroleum ether when kept at 0°C for 2dy. The stereochemistry of this major isomer was established as (26,R=H) by n.O.e. experiments. Thus when the thioamide proton (CH=S) was irradiated a 9% enhancement of the signal for the $\underline{NCH_2}CH_2$ protons was observed. Structures of the other major thioamide isomers are assigned by analogy with this case. A deutero-chloroform solution of (26, R=H) is stable at room temperature for almost 1h. after which time equilibration with (27, R=H) becomes apparent and complete

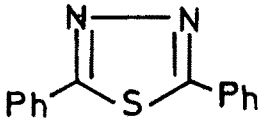
Table 2. Isomeric ratios of thioamides (26) and (27) determined by p.m.r. spectroscopy (250MHz) for deuterochloroform solutions at ca. °C

R	Ratio (26):(27)
H	1.69 : 1
Me	1.47 : 1
cyclo-C_3H_5	1.47 : 1
Ph	1.54 : 1
p-$O_2NC_6H_4$	1.45 : 1
PhCH=CH	1.40 : 1
2-furyl	1.67 : 1[a]
2-thienyl	1.54 : 1[a]

a. Ratio determined at -25°C. Spectra run at normal probe temperatures give broad signals.

equilibration is achieved after ca. 15h.

The hydrazone (16g) when heated with excess sulphur in boiling benzene for 14h. gives a mixture of thiadiazole (32) (42%) and imine (17g)(58%).



(32)

Experimental. General experimental details are as previously noted.[23] Petroleum ether refers to the fraction with b.p. 40-60°C.

General Procedure for the Preparation of Imines of α-Keto Acids

A mixture of the α-keto acid (10mmol) and primary amine (10mmol) in methylene chloride (50ml) was stirred at room temperature for 15min. during which time the α-imino acid precipitated in quantitative yield. The products were crystallised from the appropriate solvent at room temperature to avoid premature decarboxylation. The physical and spectral data are collected in Tables 3 & 4.

General Procedure for Decarboxylation of α-Imino Acids. A suspension of α-imino acid (0.4mmol) in dry benzene (25ml) or dry methylene chloride (25ml) was boiled under reflux until decarboxylation was complete (< 0.5h for benzene, typically 1-6h for methylene chloride). The solvent was then removed under reduced pressure to afford the imine in essentially quantitative yield. All the imines are known compounds.

Preparation of Deuterated α-Imino Acid (13). α-Imino acid (11b)(100mg) was dissolved in methanol-d_1 (2ml) and kept at room temperature for 10min. The solvent was then removed under reduced pressure and the process repeated a further two times to afford the product as colourless plates, m.p. 105-108°C (decomp). The p.m.r. spectrum of (13) was identical to that of the undeuterated material (11b) (the CO_2H proton was not observed in either spectrum) and the mass spectrum of (13) is identical to that of decarboxylated material (14)(below).

Decarboxylation of Deuterated α-Imino Acid (13). A suspension of α-imino acid (13)(100mg) in dry methylene chloride (5ml) was boiled under reflux for 4h. Evaporation of the solvent afforded the product (14)(83mg,100%) as a colourless oil. δ 7.65-6.64 (m,10H,ArH), 4.64 (s,2H,CH_2) and 3.66 (s,3H,OMe); m/z(%) 226 (M^+,20), 225(2), 122(9), 121(100) and 77(5).

Secondary Thioamides

General procedure

A mixture of α-imino acid (10mmol) and sulphur (100mmol, ten-fold excess) was boiled under reflux in dry benzene (50ml) for 20min., unless otherwise stated, during which time everything went into solution. The reaction mixture was allowed to cool to room temperature and MeOH (50ml) was added. The precipitated sulphur was filtered off and the filtrate evaporated under reduced pressure to afford the thioamide together with some imine. The crude thioamides were purified by preparative t.l.c. on silica gel PF_{254} + 366(Merck) eluting with 4:6 v/v Et_2O:petroleum ether followed by crystallization from an appropriate solvent. The physical and spectral data are collected in Tables 5 & 6.

Tertiary thioamides

General procedure

A mixture of α-keto acid (10mmol), secondary amine (10mmol) and sulphur (100mmol) in dry benzene (50ml) was boiled under reflux for 15min., unless otherwise stated. The reaction was left to reach room temperature and then MeOH (50ml) was added. The precipitated sulphur was removed by filtration and the filtrate evaporated under reduced pressure to give the crude product which was dissolved in ether (150ml). The ethereal solution filtered through a short column (SiO_2), the eluate evaporated, and the thioamide crystallized from an appropriate solvent. Yields, physical and spectral data are collected in Tables 7 & 8.

2,5-Diphenyl-1,3-4-Thiadiazole (32).

Benzoylformic acid (N-benzoyl)hydrazone (10mmol) was boiled under reflux in dry benzene (50ml) with sulphur (100mmol) for 14h. The reaction mixture was filtered hot to separate the precipitated benzaldehyde (N-benzoyl)hydrazone (58%). Methanol (50ml) was added to the filtrate, and the precipitated sulphur was filtered off. The filtrate was evaporated under reduced pressure to afford a pale yellowish solid which was dissolved in Et_2O (50ml) and filtered through a short column (SiO_2) for purification. Evaporation of the eluate afforded the thiadiazole (42%) which crystallized from MeOH as colourless flakes, m.p. 143-145°C (lit.[30] 140°C), ν_{max} 3020, 1500, 1460, 1430, 990, 760, 690 cm^{-1}; m/z(%) 238 (M^+,100), 135(92), 121(28), 77(52); δ 7.75 (m, 10H, ArH).

The imine was washed with carbon disulphide, dried under air suction, and then crystallised from MeOH to give colourless plates, m.p. 207-208°C (lit.[31] 210-212°C); ν_{max} 3180, 3040, 3010, 1630, 1590, 1280, 760, and 690 cm^{-1} m/z(%) 224 (M^+,6), 121(38), and 105(100), and 77(34); δ 8.33 (s, H, CH=N) and 7.35 (m, 10H, ArH).

Table 3. Physical and analytical data for α-imino acids

Cmpd.	m.p. (°C) (appearance)	Formula	Found (%) (Requires)		
			C	H	N
11a	105-107 (decomp.) (colourless plates from EtOH-petroleum ether)	$C_{15}H_{13}NO_2.H_2O$	70.35 (70.00	5.85 5.90	5.50 5.45)
11b	107-110 (decomp.) (colourless plates from EtOH-petroleum ether)	$C_{16}H_{15}NO_3.H_2O$	66.65 (66.90	6.15 5.95	4.80 4.90)
11c	110-112 (decomp.) (colourless plates from EtOH-petroleum ether)	$C_{16}H_{15}NO_2.H_2O$	70.85 (70.85	6.35 6.30	5.10 5.15)
11d	119-121 (decomp.) (colourless plates from MeOH-Et_2O	$C_{15}H_{12}N_2O_4.H_2O$	59.90 (59.60	4.85 4.65	9.35 9.25)
11e	123-125 (decomp.) (colourless rods from MeOH-Et_2O)	$C_{14}H_{13}NO_3S.H_2O$	57.75 (57.30	5.15 5.15	4.80 4.75)
16c	136-138 (decomp.) (colourless needles from MeOH-Et_2O)	$C_{15}H_{13}NO_3$	70.60 70.60	5.25 5.15	5.50 5.50)
16a[b]	124-126 (decomp.) (colourless needles from EtOH-petroleum ether	$C_{14}H_{17}NO_2.H_2O$	67.45 (67.45	7.40 7.70	5.55 5.60)
16b[b]	80-82 (decomp.) (colourless plates from CH_2Cl_2-Et_2O	$C_{12}H_{15}NO_2.H_2O$	64.70 (64.55	7.55 7.70	6.30 6.25)
16f[b]	150-152 (lit.[24] 157-157.5)(colourless needles from CH_2Cl_2	$C_{11}H_{12}N_2O_4$	55.90 (55.90	5.20 5.10	11.90 11.85)
16g[c]	167-169 (decomp.) (colourless rods from CH_2Cl_2	$C_{15}H_{12}N_2O_3$	66.95 (67.15	4.45 4.50	10.40 10.45)
16h[d]	124-125 (decomp.) (colourless amorphous solid from methylene chloride	$C_{10}H_8N_4O_2$	55.00 (55.55	3.80 3.75	26.05 25.90)

(a) reaction time 14h; (b) benzene was used as solvent; (c) 85% yield; (d) reaction time 5h.

Table 4. Spectroscopic data for α-imino acids

Cmpd.	ν_{max}(cm^{-1})	m/z(%)	($CDCl_3$/ 1 drop of TFA)
11a	3260-2380,1680,1620,1595,1560 1220,840,750,700,690,680	239 (M^+,1),195(36) 194(21),91(100),77(6)	7.55 (m-10H,ArH) 3.90 (s,2H,NCH_2)
11b	3200-2560,1680-1580,1510,1410 1250,1230,1030,830,760,720,680	225 (M-44,10),121(100), 105(5),91(7),77(10), 44(2)	7.23 (m,9H,ArH) 3.95 (s,2H,NCH_2) 3.55 (s,3H,OMe)
11c	3140-2580,1670,1615,1605,1375, 1220,810,690	209 (M-44,28),105(100), 91(9),77(11),44(11)	7.50 (m,9H,ArH) 4.00 (s,2H,NCH_2) 2.55 (s,3H,Me)
11d	3220-2500,1660-1570,1520,1340, 1220,750,670	240 (M-44,55),105(35), 91(79),77(37),44(100)	7.80 (m,9H,ArH), 4.30 (s,2H,NCH_2)
11e	3100-2500,1635,1600,1580,1490, 1460,1370,1240,1230,1050,1020, 770,750,680	231 (M-44,2),121(21), 111(100),106(17),91(17) 77(9)	7.45 (m,7H,ArH), 4.10 (s,2H,NCH_2) 3.85 (s,3H,OMe)
16c	3260-2300,1665-1570,1550,1410 1220,760,710,685,670	255 (M^+,8),211(100), 210(44),105(23),77(21), 44(21)	7.45 (m,9H,ArH), 3.80 (s,3H,OMe).
16a	3180-2500,1670-1575,1550,1410, 1220,760,710,685,670	187(M-44,15),105 (40), 77(52), 56(100),44(16)	8.28,(br s,1H, CO_2H),7.76 (m,5H,ArH),2.92 (m,1H,NCH),2.97-0.94 (m,10H, cyclohexyl-H)
16b	3300-2500,1670,1620-1530,1410, 1220,1000,990,840,760,720,690	161 (M-44,3),160(6), 105(100),91(14),77(63) 51(24),44(17)	8.30,(br s,1H, CO_2H),7.76 (m,5H,ArH),2.84 (t,2H,NCH_2),1.54 m,2H,$NCH_2\underline{CH_2}$), 1.25,(m,2H,$N(CH_2)_2$ $\underline{CH_2}Me$),0.76 (t,3H,Me)
16f	3420,3280-2600,1740,1710,1680 1585,1560,1490,1470,1390,1250, 1070,1020,700,670	236 (M^+,69),192(16), 191(58),163(72),104(50) 103(58),77(100),44(20), 29(80),28(7)	7.50,(m,5H,ArH), 4.43,(q,2H, $CO_2\underline{CH_2}Me$),1.33 (t,3H,$CO_2CH_2\underline{Me}$
16g	3240,3080-2160,1690,1635,1590, 1520,1470,1220,1100,920,780,	224 (M-44,5),121(32), 105(100),77(41),44(13)	7.35 (m,10H,ArH)
16h	3100,3060-2840,2500-2300,1600-1500,1440,1370,1250,1040,750, 700,680,630	103((100),77(6),69(39) 44(26)	9.19 (s,2H, triazolyl-H), 7.61(m,5H,ArH)

Table 5. *Physical and analytical data for secondary thioamides*

Cmpd.	Yield (%)	b.p./m.p.(°C)/ (appearance)	Formula	Found C	(%) H	(Requires) N	S
23a	70	81-82 (lit.[25] 80-82) (pale yellow needles from Et_2O-petroleum ether)	$C_{14}H_{13}NS$				
23b	76	108-109 (yellow needles from Et_2O-petroleum ether)	$C_{15}H_{15}NOS$	(70.00	5.90	5.25 5.45)	
23c	75	75-76 (pale yellow needles from Et_2O-petroleum ether)	$C_{15}H_{15}NS$	74.85 (74.65	6.25 6.25	5.60 5.80	13.30 13.30)
23d	70	100-102 (yellow needles from Et_2O-petroleum ether)	$C_{14}H_{12}N_2O_2S$	61.45 (61.75	4.40 4.45	10.30) 10.30)	
23e	79	108-109 (yellow rods from Et_2O-petroleum ether)	$C_{13}H_{13}NOS_2$	59.20 (59.20	5.05 5.00	5.30 5.30	24.55 24.35)
23f[a]	71	90-91 (pale yellow needles from Et_2O petroleum-ether)	$C_{15}H_{15}NOS$	69.65 (70.00	5.85 5.90	5.35 5.45)	
24a	80	90-91 (lit.[26] 89) (yellow plates from aq. acetone)	$C_{13}H_{17}NS$	71.45 (71.20	7.65 7.80	6.30 6.40	14.40 14.60)
24b	77	145°C/0.1mmHg (lit.[27] 165-166°C/ 0.1mmHg) (yellow oil)	$C_{11}H_{15}NS$				
24c	51	133-134 (lit.[27] 133), (yellow plates from aq. MeOH)	$C_{14}H_{13}NOS$				

a. A mixture of α-imino acid, amine and sulphur was used
b. Reaction time 5h.

Table 6 Spectroscopic data for secondary thioamides

Cmpd.	ν_{max} (cm^{-1})	m/z(%)	δ ($CDCl_3$)
23a	3300,3020,2920,1515,1490,1445, 1385,930,770,750	227 (M^+,100),121(41), 91(61),77(17)	7.56 (m,11H,ArH & NH),4.99 (d,2H,NCH_2)
23b	3350,3080,3000,2950,1595,1515 1480,1445,1375,1350,1240,1215 1020,760,720	257 (M^+,48),136(6), 77(8),121(100)	8.03 (br s,1H,NH),7.2 (m,9H,ArH) 5.01 (d,2H,NCH_2), 3.91 (s,3H,OMe).
23c	3200,3020,2910,1515,1480,1445, 1380,1335,1255,1200,920,690	241 (M^+,65),121(41), 105(100),77(10)	7.47 (m,10H,ArH & NH),4.93 (d,2H,NCH_2),2.36 (s,3H,Me).
23d	3300,1690,1590,1515,1480,1340, 1290,940,770,730,700,690	272 (M^+,100),121(82), 77(27)	7.76(m,9H,ArH), 8.04(br s,1H,NH) 5.18 (d,2H,NCH_2).
23e	3340,1515,1485,1450,1375,1310, 1240,760,720	263 (M^+,100),136(31), 127(60),121(65).	8.01 (br s,1H,NH),7.21(m,7H,ArH) 5.02 (d,2H,NCH_2),3.91(s,3H,OMe)
23f	3200,3040,2990,2900,1585,1525, 1490,1445,1380,1210,940,750, 690	257 (M^+,81),136(24), 121(100),91(59),77(24)	8.06 (br s,1H,NH),7.33 m,9H,ArH) 5.02 (d,2H,NCH_2),3.88(s,3H,OMe)
24a	3170,3020,2920,1530,1445,1380, 1215,980,770,710,690	219 (M^+,100),121(95), 77(29)	7.55 (m,6H,ArH & NH),4.54 (m,1H,NCH),2.23-1.21 (m,10H, cyclohexyl-H).
24b	3340-3160,3020,2950,1520,1480, 1445,1380,1210,765,690	193 (M^+,66),150(36), 121(100),77(24)	7.80 (br s,1H,NH),7.48 (m,5H,ArH) 3.75 (m,2H,NCH_2),1.69 (m,2H,$NCH_2\underline{CH_2}$),1.42 (m,2H,$\underline{CH_2}Me$),0.96 (t,3H,$\overline{CH_2}Me$).
24c	3150,2980,1600,1590,1510,1500, 1245,1040,820,750,690	243 (M^+,43),121(100) 77(27)	9.12 (br s,1H,NH),7.39 (m,9H,ArH),3.80 (s,3H,OMe).

Table 7. Physical and Analytical Data for Tertiary Thioamides[a]

Compound	m.p.(°C)/ (appearance)	Formula	Found / (Requires) C	H	N	S
26, R=H	73-75 (colourless plates from petroleum ether)	$C_{10}H_{11}NS$	68.00 (67.75	6.20 6.25	7.85 7.90)	
26,R=Me	106-107 (colourless needles from petroleum ether)	$C_{11}H_{13}NS$	68.90 (69.05	6.80 6.85	7.10 7.30)	
26,R=cyclo-C_3H_5	60-61.5 (colourless plates from petroleum ether)	$C_{13}H_{15}NS$	71.90 (71.85	7.00 6.95	6.45 6.45)	
26,R=Ph	110-111 (yellow prisms from aqueous MeOH)	$C_{16}H_{15}NS$	75.70 (75.85	6.00 5.95	5.60 5.55	12.90 12.65)
26, R=p-$O_2NC_6H_4$	178-180 (yellow plates from CH_2Cl_2-petroleum ether)	$C_{16}H_{14}N_2O_2S$	64.35 (64.40	4.55 4.75	9.25 9.40)	
26,R=PhCH=CH	132-134 (yellow needles from Et_2O)	$C_{18}H_{17}NS$	77.10 (77.40	6.15 6.15	5.05 5.00)	
26,R=2-furyl	34-35 (yellow prisms from petroleum ether)	$C_{14}H_{13}NOS$	68.90 (69.10	5.20 5.40	5.70 5.75)	
26,R=2-thienyl	96-97 (yellow rods from Et_2O-petroleum ether)	$C_{14}H_{13}NS_2$	64.85 (64.85	4.90 5.05	5.45 5.40)	
28, X=CH_2	75-76 (lit.[28]76) (yellow prisms from petroleum ether)	$C_{11}H_{13}NS$				
28,X=$(CH_2)_2$	63-64 (lit.[29]62-65) (yellow rods from aqueous MeOH)	$C_{12}H_{15}NS$				
28,X=CH_2O	139-141 (lit.[25]139) yellow rods from acetone)	$C_{11}H_{13}NOS$				
28, X=S	92-94 (yellow rods from petroleum ether)	$C_{10}H_{11}NS_2$	57.45 (57.40	5.35 5.30	6.65 6.70)	
24, R=Me,R^1=Ph	98-100 (lit.[27] 100-101) (lemon yellow needles from Et_2O-petroleum ether	$C_{14}H_{13}NS$				
24, R=R^1=Et	40-41 (lit.[25] 40-42) colourless needles from Et_2O-hexane)	$C_{11}H_{15}NS$				

a. Yields and reaction times are listed in Table 1.

Table 8. Spectroscopic Data for Tertiary Thioamides.[a]

Compound	ν_{max} (cm^{-1})	m/z(%)	δ ($CDCl_3$)
26, R=H	2920,2840,1500,1440, 1390,1220,1200,900,	177 (M^+,100), 132(21),117(40)	(major) 9.42 (s,1H,CHS),7.22 (m,4H,ArH),5.09 (s,2H,NCH_2), 3.95 (t,2H,NCH_2), 3.01 (t,2H, CH_2Ar), and (minor) 9.42 (s,1H, CHS), 7.18 (m,4H,ArH), 4.79 (s,2H, NCH_2), 4.20 (t,2H,NCH_2),3.93 (t,2H,CH_2Ar).
26,R=Me	3040,2990,2900,1475, 1445,1410,1340,1220, 1205,960,740,690	191 (M^+,100), 132(40),117(100) 59(19)	7.20 (m,8H,ArH, both isomers), 5.28 (s,2H,NCH_2, major), 4.83 (s,2H,NCH_2, minor),4.40 (t,2H, NCH_2CH_2Ar,minor),3.92 (t,2H NCH_2CH_2Ar,major),2.99 (m,4H, NCH_2CH_2Ar, both isomers),2.76 (s,3H,Me, minor), 2.75 (s,3H,Me, major).
26,R=cyclo-C_3H_5	3040,3000,2950,2890 1490,1450,1350,1220 760	217 (M^+,56), 132(100), 117(29) 85(12)	7.19 (m,8H,ArH, both isomers), 5.28 (s,2H,NCH_2,major),5.07 (s,2H,NCH_2,minor),4.40 (t,2H, NCH_2CH_2Ar,minor),4.14 (t,2H, NCH_2CH_2Ar,major),3.02-2.94 (m,4H,NCH_2CH_2Ar,both isomers), 2.09 (m,2H,cyclopropyl-H, both isomers), 1.34 (m,4H,cyclopropyl CH_2, major), 1.00 (m,4H, cyclopropyl CH_2,major),1.00 (m,4H, cyclopropyl CH_2, minor).

Table 8 continued

Compound	ν_{max}(cm^{-1})	m/z(%)	δ ($CDCl_3$)
26, R=Ph	3040,3000,2920,1480 1465,1435,1235,1210 770,750,700	253 (M^+,100), 132(46)121(51), 117(77),77(15)	7.11 (m,18H,ArH, both isomers), 5.37 (s,2H,NCH_2, major), 4.65 2H,NCH_2, minor), 4.47 (t,2H, $N\underline{CH_2}CH_2Ar$,minor),3.75 (t,2H, $N\underline{CH_2}CH_2Ar$,major),3.10 (t,2H, $NCH_2\underline{CH_2}Ar$,minor),2.86 (t,2H, $NCH_2\underline{CH_2}Ar$,major).
26, R=p-$O_2NC_6H_4$	3040,2940,1510,1445, 1340,1235,1215,850, 755	298 (M^+, 100), 166(10), 132(40), 117(87), 77(9)	7.59 (m,16H,ArH, both isomers), 5.38 (s,2H,NCH_2, major), 4.63 (s,2H,NCH_2, minor), 4.50 (t,NCH_2CH_2Ar,minor), 3.78 (t,$N\underline{CH_2}CH_2Ar$,major), 3.74 (t,$N\underline{CH_2}CH_2Ar$,minor),3.16 (t,$NCH_2\underline{CH_2}Ar$,major).
26, R=PhCH=CH)	3030,3010,2910,1485 1440,1240,1210,960, 740,690	279 (M^+,87), 147(31), 132(100), 117(40), 77(10)	7.45 (m,22H,ArH and olefinic-H, both isomers),5.34 (s,2H,NCH_2, major),4.98 (s,2H,NCH_2,minor), 4.46 (t,2H,NCH_2CH_2Ar, minor), 4.07 (t,2H,$N\underline{CH_2}CH_2$, major), 3.03 (m,4H,$N\underline{CH_2}CH_2Ar$, both isomers
26,R=2-furyl	2920,2825,1480,1430, 1375,1240,1210,740 720	243 (M^+,100), 132(47), 117(62), 111(22),77(6)	7.04 (m,14H,ArH, both isomers), 5.28 (s,2H,NCH_2, major), 5.06 (s,2H,NCH_2, minor), 4.33 (t,2H, NCH_2CH_2Ar, minor),4.01 (t,2H, $N\underline{CH_2}CH_2Ar$, major),3.08 (m,4H, $N\underline{CH_2}CH_2Ar$, both isomers).
26,R=2-thienyl	3040,3000,2900,1450, 1430,1340,1245,1215, 750,725	259 (M^+,100), 132(50), 127(45), 117(77),77(6)	7.23 (m,14H,ArH, both isomers), 5.28 (s,2H,NCH_2, major), 5.09 s,2H,NCH_2, minor), 4.41 (t,2H, NCH_2CH_2Ar,major),3.05 (m,4H, $NCH_2\underline{CH_2}Ar$, both isomers).
28, X=CH_2	2960,2930,2840,1490, 1445,1320,1260,760, 700	191 (M^+,100), 121(56),77(27), 70(39)	7.33 (m,5H,ArH), 3.94 (t,2H, NCH_2), 3.44 (t,2H,NCH_2), 2.00 (m,4H,2 x CH_2).
28, X=$(CH_2)_2$	3050,3000,2920,1490, 1440,1290,1240,1200, 1010,760,700	205 (M^+,100), 121(81), 84(37), 77(27)	7.31 (m,5H,ArH),4.36 (t,2H, NCH_2), 3.51 (t,2H,NCH_2), 1.78 (m,4H,2 x CH_2), 1.57 (m,2H,CH_2).
28, X=CH_2O	3040,2960,2900,1485, 1450,1425,1380,1345, 1220,1200,1100,870, 755,690	207 (M^+,95), 121(100), 86(22), 77(28)	7.32 (m,5H,ArH), 4.42 (t,2H, NCH_2), 3.86 (t,2H,NCH_2), 3.60 (m,4H, 2 x CH_2O).
28, X=S	3040,2940,2900,1470, 1450,1435,1240,765, 700	209 (M^+,51), 163(67), 121(33), 77(20), 60(100)	7.31 (s,10H,ArH, both isomers), 4.43 (s,2H,NCH_2S, minor), 4.22 (t,2H,NCH_2 minor), 3.70 (t,2H,NCH_2 major),3.13 (t,2H,CH_2S,minor), 2.96 (t,2H,CH_2S, major).
24,R=Me,R^1=Ph	3040,2900,1485,1440, 1370,1270,1210,1110, 760,695	227 (M^+,37), 121(69), 118(100) 77(30)	7.15 (m,10H,ArH),3.94 (s,3H,NMe)
24, R=R^1=Et	2980,2920,1490,1445, 1310,1250,1135,750, 695	193 (M^+,51), 121(100), 77(21)	7.29 (m,5H,ArH), 4.12 (q,2H, (NCH_2), 3.43 (q,2H,NCH_2), 1.38 (t,3H,$CH_2\underline{Me}$), 1.13 (t,3H,$CH_2\underline{Me}$).

a. Mixtures of stereoisomers about the C(S)-N bond

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