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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 15[1]. AMINE GENERATED AZAALLYL ANIONS VERSUS METALLO-1,3-DIPOLES IN CYCLOADDITIONS OF α-AMINO ACID ESTERS. FACILE REGIO- AND STEREO-SPECIFIC FORMATION OF PYRROLIDINES.

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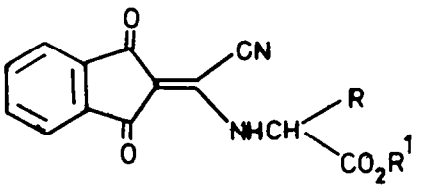
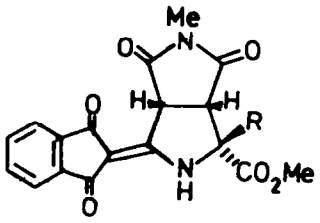
Abstract: Kinetic studies of the deprotonation of arylidene imines of alanine and phenylglycine esters by tertiary amines and pyridine and cycloaddition of the resultant 4π-azaallyl anions to N-phenylmaleimide show the expected dependance on the p-substituent in the aryl ring, e.g. p-NO_2 > H > OMe>NMe_2. A combination of metal salt (silver, lithium, or zinc) and triethylamine in THF, dipolar aprotic solvents (MeCN, DMSO, DMF) or N-methylacetamide effects regio- and stereo-specific or highly stereo-selective inter- and intra- molecular cycloaddition of imines of phenylglycine, alanine and glycine esters to a range of dipolarophiles probably via metallo-1,3-dipole formation at room temperature. Silver acetate is a more efficient and selective catalyst than lithium bromide and reactions in acetonitrile, DMSO or N-methylacetamide, are especially rapid (0.1-3.5h).

The analogy between acid and base catalysed reactions of carbonyl compounds, and of imines, was discussed in the preceding paper.[1] Cycloadditions involving Bronsted and Lewis acid catalysed stereospecific formation of azomethine ylides from imines were reported and substantial rate enhancements observed for cycloadditions in which azomethine ylide formation was rate determining. The present paper is concerned with the generation of 2-azaallyl anions from imines of α-amino esters by reaction with tertiary amines, and their subsequent trapping in cycloaddition reactions, together with the influence of various metal salts on the cycloaddition step.

Ingold[2] first studied 2-azaallyl anions but it was Kauffmann who pioneered their use in anionic cycloadditions. He showed that simple aryl substituted 2-azaallyl anions were readily available from the corresponding imines by deprotonation with lithium diisopropylamide (LDA), and that the 2-azaallyl anions undergo 4π + 2π anionic cycloaddition to unsaturated compounds containing CC, CN, NN and CS double bonds as well as CC and CN triple bonds.[3] Addition of Kauffmann's aryl azaallyl anions to the CO double bond always leads to open chain adducts.[3] Following our demonstration of the general, formal, 1,2-prototropic process in X=Y-ZH systems (imines, oximes, hydrazones)[4,5] generating 1,3-dipoles, $X=^{+}Y(H)-^{-}Z$, we extended our studies to anionic cycloadditions of imines of α-amino acid esters[6,7] and briefly reported on the use of pyridine, sodium methoxide or potassium tert-butoxide as bases. Recently we have shown that (1) undergoes a triethylamine catalysed stereospecific cycloaddition to N-methylmaleimide at room



(1) R=H, Me, Ph



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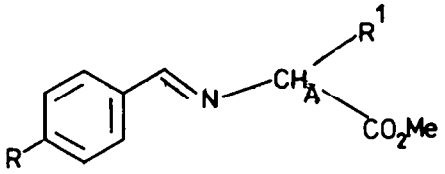
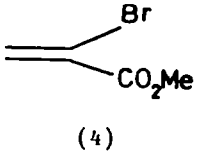


(3) a. R^1 = Ph
b. R^1 = Me



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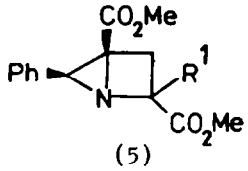

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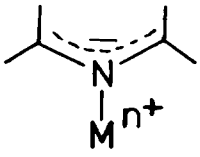

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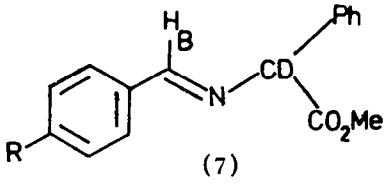

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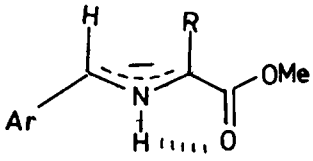
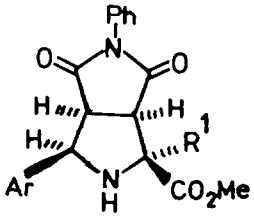
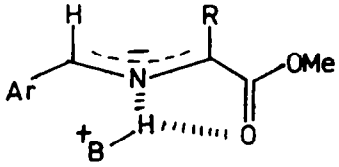


(8) a. R=Ph
b. R=Me
c. R=H



(9) a. Ar=p-RC_6H_4, R^1=Ph
b. Ar=p-RC_6H_4, R^1=Me
c. Ar=2-naphthyl, R^1=H



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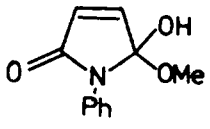

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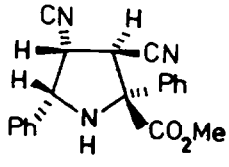

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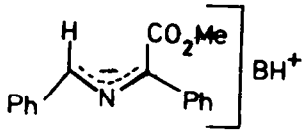


(13)

temperature giving (2) in >70% yield.[8] Others[9,10] subsequently extended Kauffmann's conditions (LDA, THF, -80 to +20°C) to imines of α-amino esters (3) and provided an elegant synthesis of the 3/4 fused ring system (5) by using (4) as the dipolarophile. We had earlier suggested Kauffmann's anionic cycloadditions might be examples of metallo-1,3-dipoles (6, M=Li⁺),[11] and have subsequently provided examples of a range of such species.[1,12,13] We now report studies on amine catalysed formation of 2-azaallyl anions from (3) and the influence of added silver, lithium and zinc salts, and solvent on their reactivity.

Cycloadditions of 2-azaallyl anions

We find that imines (3a) undergo regiospecific deuteriation of H_A giving (7) when heated in 1:1 v/v [$^2H_4$]methanol-[$^2H_8$]toluene (Table 1). Deuteriation at H_B was not detected. The rate of deuteriation (Table 1) follows the order of expected acidity of H_A and during the exchange reactions some transesterification occurred producing (7, CO_2CD_3) (p.m.r.). The rate order (Table 1) is precisely the reverse of the cycloaddition rate of (3a) to N-phenylmaleimide (NPM) under thermal activation in toluene.[14] In this latter case the dipole (8a) is involved. The deuteriation rate only increases ca. three fold (Table 1) in going from (3a, R=OMe) to (3a, R=NO_2) indicating either the effect of R on the pK_a of H_A is not substantial under these conditions or that a general acid-general base catalysed process is operating. The regiospecificity of the exchange process mirrors that observed in the base catalysed alkylation and Michael addition reactions of imines of α-amino acid esters first observed by Stork[15] and subsequently extended by others.[7,16]

TABLE 1

Deuterium incorporation rates for imines (3a) giving (7) in 1:1 v/v [$^2H_4$] methanol-[$^2H_8$]toluene.[a]

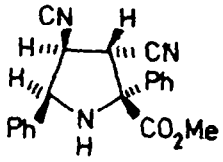
Imine	k x 10^5(sec^{-1})[b]
R=OMe	3.47
R=H	3.60
R=CN	7.00
R=NO_2	11.40

a. Exchange rate determined for 0.2 M solutions in sealed n.m.r. tubes heated in a thermostated oil bath at 110 ± 0.5°C.

b. Pseudo first order rate constant.

A study of the influence of amines on the rate of cycloaddition of (3a) and (3b) to NPM was undertaken and the results are collected in Table 2. The reactions were clean and stereospecific and single products (9a) or (9b) were formed in each case. The stereochemistry of the cyclo-adducts is identical to that observed for processes involving the prototropically generated azomethine ylides (8a) and (8b)[14,17] and implicates cycloaddition of species with some configuration determining interaction such as (10).[8]

The rate of cycloaddition of (3a) (Table 2) shows the expected order for a process involving deprotonation with an overall eighteen fold increase in rate in going from R=NMe_2 to R=NO_2. A similar trend is observed for (3b) with an overall thirty fold increase in rate in going fromR=OMe to R=CN. The data in Table 2 compare with a value of k x $10^5 sec^{-1}$ for (3a, R=H) of 9.6[14] and for (3b, R=H) of 5.57,[18] both in toluene at 105°C, for reaction which involve a formal 1,2-prototropic shift generating the azomethine ylides (8a) and (8b). The effect of the p-substituent in (3a) and (3b) on the rate of cycloaddition in the presence of amines is precisely the reverse of that observed for processes involving 1,2-prototropy generating (8a) and (8b).[14] An interesting observation in Table 2 is that the cycloaddition of (3b, R=H) to NPM is faster in toluene containing 1 mol of pyridine (k = 8.02 x $10^{-5} sec^{-1}$) than in neat pyridine (k=1.79 x $10^{-5} sec^{-1}$).



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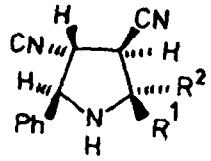
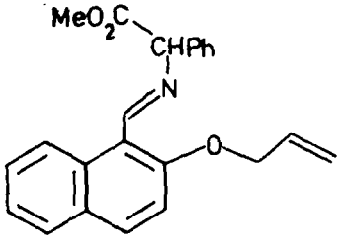


(15) a. R^1= CO_2Me, R^2= Ph
b. R^1= Ph, R^2= CO_2Me



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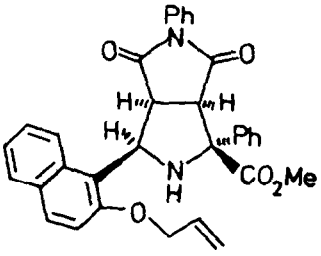
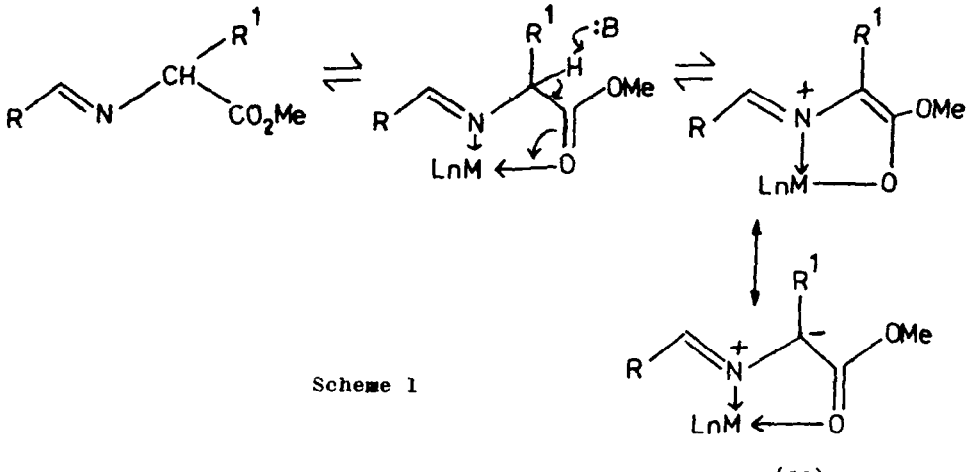


(17)

$$M(OH_2)_x^{n+} \rightleftharpoons M(OH_2)_{x-1}(OH)^{(n-1)+} + H^+$$

(18) (19)



Scheme 1

(20)

TABLE 2

Amine catalysed cycloaddition of imines (3) to N-phenylmaleimide at 95°C.[a]

Imine	Solvent[b]	Base[c]	k x 10^5(sec^{-1})
3a, R=NMe_2	pyridine	-	5.55
3a, R=OMe	pyridine	-	9.24
3a, R=H	pyridine	-	28.4
3a, R=NO_2	pyridine	-	101.0[d]
3b, R=OMe	pyridine	-	1.59
3b, R=H	pyridine	-	1.79
3b, R=CF_3	pyridine	-	12.90
3b, R=CN	pyridine	-	48.1
3b, R=H	toluene	$n\text{-}Bu_3N$	2.80[e]
3b, R=H	toluene	Et_3N	4.68
3b, R=H	toluene	pyridine	8.02
3b, R=H	toluene	DABCO[f]	30.30[e]

a. All reactions were performed on 0.2 M solutions of imines (3) and NPM. The solutions were flushed with argon and sealed in an n.m.r. tube. Kinetics were measured in the probe of a Bruker WH90 spectrometer, spectral width 1000 Hz, 4 K data points, temperature accurate to ±0.5°C.

b. All solvents were fully deuteriated.

c. 1 Mol. of base added.

d. Approximate value due to the reaction being very fast at 95°C.

e. It was difficult to reproduce these rates presumably due to polymerisation of the dipolarophile. The results are the average of four successful reactions. In addition there were four failures.

f. Diazabicyclooctane.

This presumably reflects the enhanced azaallyl anion-protonated base intermolecular hydrogen bonding (10) in toluene compared to pyridine. In a preparative experiment, heating (3a, R=H) with NPM in pyridine (110°C, 15h) gave a quantitative yield of (9a, R=H).

Attempts to develop the amine catalysed cycloadditions of (3) into a general room temperature procedure as achieved for the acid catalysed cycloadditions[1] gave variable results. Thus (3a, R=H) and (3b, R=H) react with NPM in methanol at room temperature, over 24 and 48h respectively, in the presence of 1mol of DABCO to give (9a, R=H) (56%) and (9b, R=H) (46%), together with other products including (11). An analogous reaction of (3a, R=H) in tetrahydrofuran (THF) using triethylamine (1mol) as base gave (65%), a 9:1 mixture of (9a, R=H) and its exo-isomer. The imine (3a, R=H) and fumaronitrile react [MeOH, 25°C, DABCO (1mol)] to give (12) (25%), together with a complex mixture of other products. Cycloadduct (12) does not arise from the expected kinetic azaallyl anion (10) but from the stereomutated species (13) showing that in protic solvents hydrogen bonding of BH^+ to the solvent reduces its configuration holding ability via (10). This result, together with the previously mentioned faster rate of cycloaddition of (3b, R=H) to NPM in toluene containing 1mol of pyridine compared to neat pyridine, indicates that hydrogen bonded azaallyl species such as (10) are the reactive 4π-components in these cycloadditions. The structure of (12) was assigned by n.O.e. studies (see experimental section) and by comparison with the products from the reaction of (3a, R=H) with fumaronitrile (toluene, 110°C, 48h) in the absence of base. This latter reaction gives a 3:14:1:1 mixture of (12), (14), (15a) and (15b). The tendency of the corresponding 1,3-dipole (8a) to undergo varying degrees of stereomutation in reactions with dipolarophiles less active than maleimides has been previously noted.[6,19,20] The imine (3b, R=H) failed to give any identifiable cycloadduct when reacted (MeOH, 25°C, 48h) with fumaronitrile and DABCO (1mol), and (16) failed to

undergo intramolecular cycloaddition[20] under the same conditions. Imine (16)does however react with NPM under identical conditions to give (17) (95%) showing the azaallyl anion is being generated. A number of other dipolarophiles (ethyl diazodicarboxylate, dimethyl acetylenedicarboxylate, dimethyl fumarate), bases (NEt_3, LDA, n-BuLi) and solvents (MeCN, THF) were studied but, in general, yields were poor apparently due to base induced polymerisation of the dipolarophiles.

Metal salt-triethylamine catalysed cycloadditions

We had previously found that weak Lewis acids such as zinc, silver, lithium and magnesium acetates, lithium bromide, and silver tosylate, catalyse regio- and stereo-specific cycloadditions of arylidene imines of α-amino acid esters to a range of dipolarophiles at 80-110°C.[1] It was suggested that these Lewis acid catalysed processes are due to both traces of Bronsted acids produced by the well known ionisation of aquo-cations (18) → (19),[21] and to the formation of metallo-1,3-dipoles (20) (Scheme 1).[1]

Metallodipole formation (Scheme 1) involves coordination of the metal ion to the nitrogen atom and carboxylate group of the imine followed by deprotonation with the metal counter-ion, adventitious water, or uncomplexed imine acting as the base. The scheme suggests that addition of tertiary amines should promote metallodipole formation and offered the possibility that the metallodipole would not induce polymerisation of dipolarophiles. Accordingly this approach was studied with three types of imine (3a-c, R=H) (Table 3).

A range of metal salts in conjuction with triethylamine were found to effect cycloaddition of (3a-c, R=H) to NPM, methyl acrylate and fumarate esters at room temperature (Table 3). The reactions occurred comparatively slowly in THF (20-48 h) but rapidly (0.2-2.5 h) in acetonitrile (Table 3). Yields of cycloadducts are good to excellent and the cycloadditions occur readily with catalytic amounts of the more effective catalysts such as silver acetate and lithium bromide. The cycloadditions involve the stereospecific formation of either metallodipoles (20) (Scheme 1) or some related species and show little, if any, sign of dipole stereomutation. The reactive intermediates undergo regio- and stereo-specific cycloaddition to NPM, methyl acrylate and fumarate esters when the most favourable catalysts are used (Table 3). The low temperature of the reactions is believed to be the major contributing factor to the regio- and stereo-specificity rather than any specific coordination of dipolarophile to the metallodipole or related species.

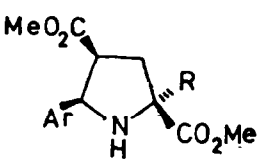
The thermal reaction of (3a, R=H) with diphenyl fumarate (toluene, 110°C, 48 h) gives a 9:2:2:1 mixture of (22a), (23a), (24) and (25),[19] involving an 11:3 ratio of dipoles (8, R=Ph) and (29, R=Ph) (Scheme 2). The tendency of the kinetic dipole (8, R=Ph) to stereomutate in cycloadditions involving dipolarophiles less active than maleimides has been noted and discussed by us previously.[19,20] The use of low temperatures in the metal salt-triethylamine method retards or suppresses the stereomutation (Table 3). The reaction (MeCN, 0.5 h, 25°C) of imine (3b, R=H) with methyl acrylate in the presence of silver acetate (1.5) and triethylamine (1.0) to give (21b, 80%) (Table 3) compares with the same reaction (MeCN, 80°C, 12-15 h) in the presence of 1 mol. of silver acetate, lithium bromide or lithium acetate but with no triethylamine which gives (21b) in essentially quantitative yield.[1] In contrast, the same reaction (MeCN, 0.5 h, 25°C) in the presence of lithium bromide (1.5 mol) and triethylamine (1.0 ml) gives an approximately 1:1 mixture of (21b) and Michael adduct (26) (Table 3). Michael adduct (26) was prepared from imine (3b, R=H) and methyl acrylate, using BTAM as the base, as previously described[7], and recycled through the reaction. Cyclisation to (21b) did not occur, showing that (26) is not a precursor of (21b). The reaction of (3b, R=H)

with dimethyl fumarate in the presence of zinc bromide-triethylamine gives a 2.7:1 mixture (90%) of (23b) and (22b) (Table 3) whilst the thermal reaction (toluene, 110°C, 48 h) gives a 1:2.4 mixture of (23b) and (22b).[19] Moreover, the same reaction using silver acetate-triethylamine or lithium bromide-triethylamine (Table 3) gives (23b) as the sole product i.e. the stereochemical preference is reversed in the metallodipole case. The formation of (22b) in the zinc bromide reaction suggested that the Lewis acid might be effecting equilibration of (23b) and (22b) via a 1,3-cycloreversion. We have previously noted a similar effect of zinc salts on cycloadditions involving nitrones.[22] When (23b) was recycled through the reaction conditions [$ZnBr_2$(1.5 mol), NEt_3(1.1 mol), THF, 25°C, 72 h] epimerisation occurred giving 14:12:4.5 mixture of (23b) and two new isomers neither of which was (22b), i.e. no 1,3-cycloreversion was occurring under these conditions.

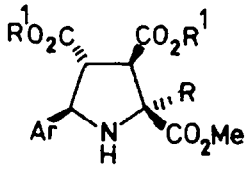
The azomethine ylides (8c) derived from glycine imines are particularly sensitive to stereomutation (8, R=H) (29, R=H) (Scheme 2) in cycloadditions with dipolarophiles less active than maleimides,[6] and the cycloadducts themselves are prone to epimerisation.[6] The mild conditions of the metal salt-triethylamine catalysed cycloadditions are thus particularly valuable in cycloadditions involving glycine imines. The results of cycloadditions involving the glycine imine (27) (Table 3) show excellent yields of single isomers formally derived from dipole (20, R = 2-naphthyl, R^1=H) (Scheme 1). Thus methyl acrylate and (27) give a single cycloadduct (21c) with silver acetate (1.5 mol or 0.15 mol)-triethylamine rapidly and cleanly at 25°C (Table 3), whilst the thermal process (toluene, 110°C) gives a mixture of four stereoisomeric cycloadducts[6] arising from both the kinetic dipole (8, R=H) and the stereomutated dipole (29, R=H) (Scheme 2). Lithium bromide is a less useful catalyst in the case of glycine imines because of its hygroscopic nature. It reacts with adventitious water and promotes Bronsted acid catalysed processes (cycloadditions and epimerisations) via (18) → (19). Thus when (27) and methyl acrylate are reacted (MeCN, 25°C, 0.5 h) in the presence of lithium bromide (1.5 mol) and triethylamine (1.0 mol) a 1:1 mixture of cycloadduct (21c) and its Michael adduct (28) is obtained (Table 3). Moreover silver acetate is a much more efficient catalyst than lithium bromide since substantial amounts of silver acetate remain undissolved in THF and acetonitrile whilst lithium bromide is completely soluble in these two solvents.

Mechanism

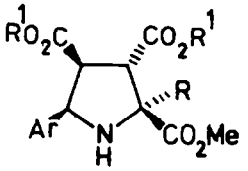
The d^{10} silver cation is a soft, polarisable, class b cation and interacts strongly with acetonitrile.[23] This interaction is believed to be a case of synergistic electron donation and back bonding to the π* orbitals of acetonitrile. In contrast, the lithium cation is a hard class a cation with strong electrostatic interactions with polar solvents but lacking the specific silver ion-acetonitrile interaction. Both series of metal salts are however effective catalysts in acetonitrile suggesting the solvent effect derives mainly from its polarity and non-protic nature. We therefore briefly surveyed other solvents for the cycloaddition of (27) (1 mol) and methyl acrylate (2 mol) to give (21c), in the presence of silver acetate (1.5mol) and triethylamine (1mol) at room temperature. The experiments were performed in n.m.r. tubes using fully deuteriated solvents. The approximate times for complete reaction were 10 min. (DMSO), 30 min. (acetonitrile) and 35 min. (DMF). A larger scale reaction in N-methylacetamide was followed by removing aliquots and was complete in less than 10 min. Cycloadduct (21c) was the sole product and all the reactions were clean. When the reaction [$^2H_6$]DMSO was repeated using lithium bromide (1.5mol) in place of silver acetate no reaction was apparent after 30 min. whilst after 20h the reaction had proceeded to ca.40% giving a ca.1:1 mixture of two products, (21c) and an isomer,



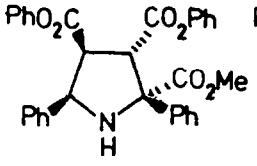
(21) a. Ar=R=Ph
b. Ar=Ph,R=Me
c. Ar=2-naphthyl, R=H



(22) a. Ar=R=R^1=Ph
b. Ar=Ph,R=R^1=Me
c. Ar=2-naphthyl, R=H, R^1=Me



(23) a. Ar=R=R^1=Ph
b. Ar=Ph, R=R^1=Me
c. Ar=2-naphthyl, R=H, R^1=Me



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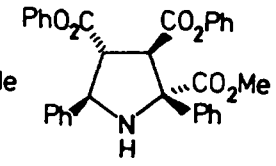

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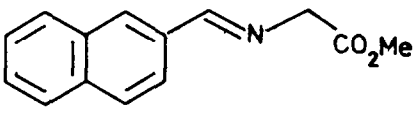

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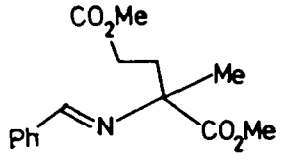

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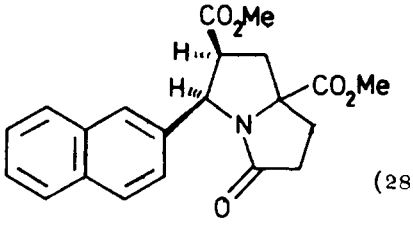

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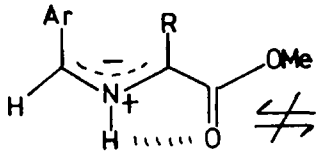

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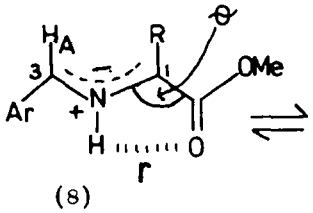

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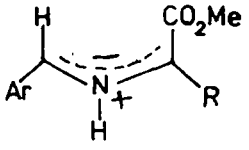
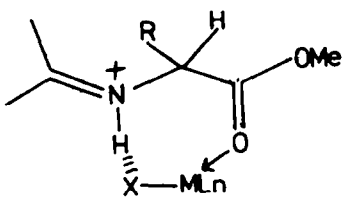


(29)

Scheme 2



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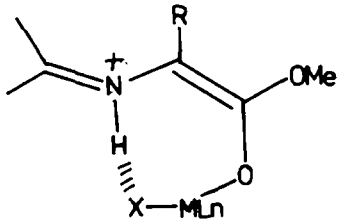


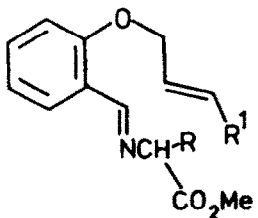
(32)

TABLE 3

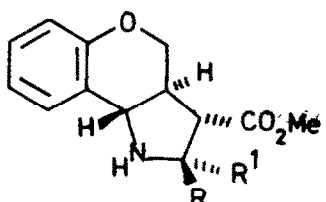
Cycloaddition of imines (3a-b) and (27) and dipolarophiles at room temperature in the presence of metal salts and triethylamine.

Imine	Metal Salt (mol)	NEt_3 (mol)	Dipolarophile[a]	Solvent	Time (h)	Product (%)[b]
3a, R=H	LiI(1.5)	1.2	NPM	THF	20	9a, R=H(60)
3a, R=H	$ZnBr_2$(1.5)	1.2	NPM	THF	30	9a, R=H(75)[c]
3a, R=H	$LiOAc.2H_2O$ (1.5)	1.2	NPM	THF	30	9a, R=H(90)[c]
3a, R=H	AgOAc(1.5)	1.0	NPM	MeCN	0.5	9a, R=H(71)
3a, R=H	LiBr(1.5)	1.0	NPM	MeCN	0.2	9a, R=H(100)
3a, R=H	AgOAc(1.5)	1.0	MA	MeCN	0.5	-[d]
3a, R=H	LiBr(1.5)	1.0	MA	MeCN	0.5	21a(100)
3a, R=H	LiBr(1.5)	1.2	FP	THF	48	22a(85)[e]
3a, R=H	AgOAc(1.5)	1.0	FP	MeCN	0.5	22a,25,23a
3a, R=H	LiBr(1.5)	1.0	FP	MeCN	0.5	22a(20)
3b, R=H	AgOAc(0.1)	0.1	NPM	THF	48	9b, R=H(52)
3b, R=H	AgOAc(0.1)	0.1	NPM	MeCN	3.5	9b, R=H(59)
3b, R=H	LiBr(0.1)	0.1	NPM	MeCN	3.5	9b, R=H(55)
3b, R=H	AgOTs(1.5)	1.0	MA	THF	48	21b(81)
3b, R=H	AgOAc(1.5)	1.0	MA	MeCN	0.5	21b(80)[g]
3b, R=H	LiBr(1.5)	1.0	MA	MeCN	0.5	21b,26 (90)[h]
3b, R=H	$ZnBr_2$(1.5)	1.1	FE	THF	72	22b,23b(90)[i]
3b, R=H	AgOAc(1.5)	1.0	FE	THF	36	23b(90)
3b, R=H	AgOAc(1.5)	1.0	FE	MeCN	0.67	23b,22b(85)[j]
3b, R=H	LiBr(1.5)	1.5	FE	MeCN	0.67	23b,22b(89)[k]
27	LiBr(0.1)	0.1	NPM	THF	24	9c(62)
27	AgOAc(0.1)	0.1	NPM	MeCN	9.5	9c(65)
27	$LiOAc.2H_2O$(1.5)	1.0	MA	THF	40	21c(76)[l]
27	AgOAc(1.5)	1.0	MA	THF	16	21c(87)
27	AgOAc(1.5)	1.0	MA	MeCN	0.5	21c(100)
27	AgOAc(0.15)	0.1	MA	MeCN	2.5	21c(87)
27	LiBr(1.5)	1.0	MA	MeCN	0.5	21c,28(71)[m]
27	AgOAc(1.5)	1.0	FE	THF	16	23c(89)
27	AgOAc(0.15)	0.1	FE	MeCN	2.5	23c,22c(82)[n]
27	LiBr(1.5)	1.0	FE	MeCN	0.5	23c,22c(71)[o]

a. NPM = N-phenylmaleimide, MA = methyl acrylate, FP = diphenyl fumarate, FE = dimethyl fumarate.
b. Isolated yields.
c. A trace amount (<5%) of the corresponding exo-adduct was also detected.
d. Imine recovered unchanged.
e. Trace amounts (<5%) of three other isomers detected.
f. 4:3:1 mixture
g. Plus 20% starting material.
h. 1.2:1 ratio of (21b) to (26a).
i. 1:2.7 ratio of (22b) to (23b).
j. 7:1 ratio of (23b) to (22b).
k. 6:1 ratio of (23b) to (22b).
l. comprises a 4.5:1 mixture of (21c) and an unidentified product
m. 1:1 ratio of (21c) to (26b).
n. 5:1 ratio of (23c) to (22c).
o. 7.5:1 ratio of (23c) to (22c).



(33) a. R=Me, R^1=CO_2Me
b. R=Ph, R^1=CO_2Me
c. R=Me, R^1=H
d. R=Ph, R^1=H



(34) a. R=Me, R^1=CO_2Me
b. R=Ph, R^1=CO_2Me

believed to be either the C(4) or C(2) epimer of (21c). Moreover, substantial amounts of silver acetate remained undissolved in all solvents whilst lithium bromide dissolved completely in DMSO. Thus silver acetate is both a more efficient and a more selective catalyst than lithium bromide and DMSO or N-methylacetamide are the solvents of choice. However, it should be noted that a reported magnesium salt catalysed reduction of imines in acetonitrile was subsequently shown to involve iminium ions generated by trace amounts of water in dry acetonitrile by (18) → (19) ($M=Mg^{2+}$).[24] In our case whilst similar Bronsted acid equilibria are undoubtedly occurring, the reactive intermediates in the metal salt-triethylamine catalysed reactions exhibit enhanced reactivity compared to the species generated by Bronsted acids[1], i.e. the species generated by the metal salt-triethylamine system undergo fast cycloaddition to acrylate and fumarate esters at room temperature. In the presence of metal salts and absence of triethylamine the reactions occur much more slowly even on heating to 80°C.[1] Similarly the same reactions using 10% v/v acetic acid-acetonitrile or acetic acid (1.5mol)-triethylamine (1.0mol) in acetonitrile are much slower than the reactions using the metal salt-triethylamine combination as catalyst. Mechanistic speculation must thus invoke a role for both the metal salt and the base, and account for stereospecific dipole formation. The metallodipole (20) (Scheme 1) would fulfil these requirements but so would species such as (31) → (32) where X is the metal counter-ion or a hydroxide ion arising from dissociation of coordinated water, i.e. (18 → 19). Our preference is for the metallo-1,3-dipole (20) (Scheme 1) but further speculation on what are clearly potentially complex equilibria is not warranted with our current results. However the powerful synthetic utility of the metal salt-triethylamine methodology is unquestionable.

In previous papers in this series we have discussed the stereomutation of the kinetic dipole (8) (Scheme 2)[4,17,20] as a function of the R group in (8) and the dipolarophile (rate of cycloaddition), and provided circumstantial evidence that the stereomutation involves rotation about the C(1)-N bond to give (29) rather than rotation about the C(3)-N bond to give (30) (Scheme 2). The kinetic dipole (8, R = alkyl) is essentially inert to stereomutation at temperatures up to 140°C whilst the kinetic dipole (8, R=Ph) undergoes stereomutation at temperatures $\geqslant$ 80°C when the dipolarphile is less active than maleimides i.e. maleate and fumarate esters,[19] acrylate esters and acrylonitrile.[6] The tendency of (8, R=Ph) to equilibrate with (29, R=Ph) was rationalised as arising from a combination of steric interactions between R and H_A in (8) (Scheme 2) and partial charge delocalisation over the two aryl rings at the termini of the dipole which reduces the bond order in the central C-N-C moiety and hence lowers the barrier to rotation-stereomutation. Similar arguments can be applied to metallodipoles (20) or to (32). However, the above rationale does not account for the observed sensitivity of (8, R=H) to stereomutation,[6] since(8, R=H) lacks both the steric and electronic effects thought to be important in stereomutation of (8, R=Ph). A possible explanation is that alkyl substitution (8, R = alkyl) results in steric interaction between H_A and R (Scheme 2) which in turn results in a reduction of the angle θ (Scheme 2) and enhances the hydrogen bonding by reducing the carbonyl oxygen to NH distance r (Scheme 2). Thus in (8,R=H) the angle θ and r are at a maximum and hydrogen bonding is at its weakest.

Intramolecular Cycloadditions

The metal salt-triethylamine approach was also successful in effecting intramolecular cyclisations rapidly at room temperature. Thus (33a) cyclised (MeCN, 25°C, 2 h) to (34a) in quantitative yield (pmr) (isolated yield 80%) whilst (33b) gave (34b) (88%) under the same conditions. Attempts to cyclise (33c) and (33d) under the same conditions were unsuccessful.

EXPERIMENTAL

General experimental details were as previously noted.[14] Analytical grade silver, lithium and zinc salts were used without purification. Liquid bases were distilled from potassium hydroxide and stored over molecular sieves. THF was dried with, and distilled from, lithium aluminium hydride. Acetonitrile was distilled from phosphorous pentoxide and stored over molecular sieves (4A). Imines were prepared as previously described[14,17] except as noted below. Petroleum ether refers to the fraction with b.p.40-60°C.

Imines

Methyl 2-naphthylideneglycinate (27). Prepared by method B as described previously.[14] The product (79%) crystallised as colourless plates from ether-petroleum ether, m.p. 89-90°C (Found: C, 73.80; H, 6.15; N, 6.35. $C_{14}H_{13}NO_2$ requires C, 74.00; H, 5.75; N, 6.15%); δ8.38 (s, 1H, CH=N), 8.2-7.4 (m, 7H, ArH), 4.4 (s, 2H, CH_2), and 3.8 (s, 3H, OMe); m/z (%) 227 (M^+, 47), 168(100), 167(21), 154(28), 141(87) and 139(15).

Methyl N-[2-(3-carbomethoxyprop-2-enyl)oxy]benzylidenealaninate (33a). A mixture of alanine methyl ester hydrochloride (1.4g, 1.0mmol), anhydrous magnesium sulphate (2g) and triethylamine (1.1g, 1.1mmol) in dry methylene chloride (50ml) was stirred for 10 min. and then a solution of 2-(3-carbomethoxyprop-2-enyl)oxybenzaldehyde (2g, 0.9mmol)[20] in dry methylene chloride (10ml) was added. The resulting mixture was stirred at room temperature for 16h. and then filtered. The filtrate was washed with water (2x50ml), dried ($MgSO_4$), and evaporated to leave a thick yellow oil (2.6g, 82%) which could not be distilled and which was used without further purification for the next stage. δ 8.8 (s, 1H, CH=N), 8.0-6.9 (m, 5H, ArH and CHCHCO), 6.2 (m, 1H, =CHCO), 4.8 (m, 2H, OCH_2), 4.2 (q, 1H, CHMe), 3.7 (s, 3H, OMe), and 1.5 (d, 3H, Me); m/z(%) 305 (M^+, 8), 246(100), 218(18), 216(31), 171(19) and 132(34).

Base Catalysed and Thermal Reactions

Methyl 2, c-4, 7-triphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (9a, R=H). (a) Methyl N-benzylidenephenylglycinate (50 mg, 0.2 mmol) and NPM (35 mg, 0.2 m mol) were dissolved in dry [$^2H_5$]pyridine (1 ml) and heated at 110°C for 1.5 h in a sealed n.m.r. tube. Removal of the solvent afforded the product (84 mg, 100%) indentical to that described previously.[14] δ7.7-7.1 (m, 15H, ArH), 4.42 (d, 1H, J 9.1 Hz, 4-H), 4.23 (d, 1H, J 7.3 Hz, 1-H), 3.78 (s, 3H, OMe), 3.50 (dd, 1H, 5-H), and 3.25 (br s, 1H, NH).

(b) Methyl N-benzylidenephenylglycinate (2.53 g, 1.0 mmol), NPM (1.73 g, 1.0 m mol) and DABCO (1.12 g, 1.0 mmol) were dissolved in dry methanol (100 ml) and the solution stirred at room temperature for 16 h during which time the product precipitated. The product (2.4 g, 56%), m.p. 246-248°C (lit.[17] m.p. 238-240°C) was identical to that described above.

Methyl 2-methyl-c-4, 7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (9b, R=H). Methyl N-benzylidenealaninate (1.5 g, 7.8 mmol), NPM (1.35 g, 7.8 m mol) and DABCO (880 mg, 7.8 mmol) were dissolved in dry methanol (100 ml) and stirred for 16 h at room temperature during which time the product (1.2 g, 46%) crystallised out as colourless rods, m.p. 221-223°C (lit.[17] 220-222°C).

Methyl 2,5-diphenyl-3,4-dicyanopyrrolidine-2-carboxylate (12)-(15). (a) A solution of methyl N-benzylidenephenylglycinate (1.9 g, 7.5 mmol), fumaronitrile (590 mg, 7.5 mmol) and DABCO (840 mg, 7.5 mmol) in dry methanol (75 ml) was stirred at room temperature for 16 h during which time the product (12) (560 mg, 22%) crystallised out as colourless rods, m.p. 186-187°C. This product was identical to the second most abundant isomer from the thermal reaction (below).

(b) (with W.J. Warnock). A solution of methyl N-benzylidenephenylglycinate (2m mol) and fumaronitrile (2 mmol) in toluene (10 ml) was boiled under reflux for 48 h. Evaporation of the solvent left a pale yellow gum (100%) whose p.m.r. spectrum showed it to comprise a 14:3:1:1 mixture of (14), (12), (15a) and (tentatively) (15b). Crystallisation from ether-petroleum ether afforded a pure sample of (12) whilst crystallisation from ether-petroleum ether-benzene afforded a sample containing the bulk of (14), (12) and (15b). Evaporation of the mother liquor in this latter case afforded a 5:1 mixture of (14) and (15a) as a colourless gum. This mixture was used for n.O.e. experiments to assign stereochemistry to both (14) and (15a). (Found (mixed isomers): C, 72.50; H, 5.30; N, 12.65. $C_{20}H_{17}N_3O_2$ requires C, 72.50; H, 5.15; N, 12.7%); m/z (%) (mixed isomers) 331(M^+, 0.5),273(20), 272(100), 193(14) and 104(11).

(14) δ7.38-7.70 (m, 10H, ArH), 4.42 (br, d, 1H, J 9.0 Hz, 5-H), 3.88 (d, 1H, J 8.7 Hz, 3-H), 3.84 (s, 3H, OMe) and 3.39 (t, 1H, 4-H).

(12) Colourless prisms from ether-petroleum ether, m.p. 184-186°C. δ7.40-7.74 (m, 10H, ArH), 4.78 (dd, 1H, J 8.8 and 4.6 Hz, 5-H), 3.93 (t, 1H, J 8.6 Hz, 4-H), 3.85

(s, 3H, OMe), 3.48 (d, 1H, J 8.6 Hz, 3-H) and 3.13 (d, 1H, J 4.5 Hz, NH). (15a) 7.38-7.70 (m, 10H, ArH), 5.02 (br, d, 1H, J 6.0 Hz, 5-H), 4.59 (d, 1H, J 4.0 Hz, 3-H), 3.88 (s, 3H, CO_2Me) and 3.60 (dd, 1H, 4-H).

(15b) The presence of this isomer was inferred from the presence of the following p.m.r. signals 4.51 (d, 1H, 5-H), 4.32 (d, 1H, 3-H) and 3.20 (dd, 1H, 4-H).

^{1}H NOEDS Stereochemical Assignments

Compound	Proton Irradiated	n.O.e. enhancement (%)			
		H-3	H-4	H-5	ArH
14	H-3[a]				
	H-4	1		1	5
	H-5	2	2		8
12	H-3		4		13
	H-4	2		10	
	H-5		10		9
15a	H-3		3		9
	H-4	2		5	
	H-5		7		11

a. Signal not sufficiently resolved to irradiate.

Methyl 2,7-diphenyl-c-4-[1-(2-allyloxynaphthyl)]-6,8-dioxo-3,7-diazobicyclo[3.3.0]-octane-r-2-carboxylate (17). A solution of methyl N-[1-(2-allyloxynaphthylidene)] phenylglycinate (36 mg, 0.1 mmol), NPM (17 mg, 0.1 mmol) and DABCO (11 mg, 0.1 mmol) in [$^2H_4$]methanol (1 ml) was kept at room temperature and monitored by p.m.r. spectroscopy. Initially a substantial amount of the hemiacetal (11) was present but this gradually disappeared with a corresponding increase in product signals. After 10 h the reaction was complete. Evaporation of the solvent left a colourless solid comprising (17) and DABCO. δ7.89-7.21 (m, 16H, ArH), 6.02 (m, 1H, CH=CH_2), 5.83 (d, 1H, NH), 5.21 (m, 3H, CH=CH_2 and 4-H), 4.65 (m, 2H, OCH_2), 4.31 (d, 1H, J 7.7 Hz, 1-H), 3.81 (s, 3H, OMe), 3.61 (dd, 1H, H-5) and 2.78 (DABCO signal). This product was identical with that described previously.[1]

Metal Salt-Triethylamine Catalysed Reactions

General Procedure. Imine (1 mol) and dipolarophile (1.1 mol for fumarate esters and NPM, 2.0 mol for methyl acrylate) were dissolved in dry THF or acetonitrile and the appropriate metal salt added (for molar ratio see Table 3), followed by triethylamine (for molar ratio see Table 3). The mixture was stirred at room temperature for the time noted in Table 3 and then quenched with aqueous ammonium chloride. The mixture was extracted with ether, the ether extract washed once with brine, dried ($MgSO_4$) and evaporated. The crude product was examined by p.m.r. (250 MHz) and, where appropriate, isomers ratios determined by integration.

Dimethyl 2, c-5-diphenyl-r-2, c-4-pyrrolidine dicarboxylate (21a). Obtained as colourless needles, m.p. 100-102°C, from ether-petroleum ether (Found: C, 70.90; H, 6.45; N, 4.3. $C_{20}H_{21}NO_4$ requires C, 70.80; H, 6.25; N, 4.15%); δ7.81-7.22 (m, 10H, ArH), 4.52 (d, 1H, J 7.4 Hz, 5-H), 3.72 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.19 (m, 2H, 3-H, 4-H), and 2.58 (dd, 1H, J 6.7 Hz, 12Hz, 3-H). m/z (%) 339 (M^+, 0.1) and 280(100).

Diphenyl 2, c-5-diphenylpyrrolidine-r-2, c-methoxycarbonyl-3,t-4-dicarboxylate (22a) (a) The p.m.r. spectrum of the crude reaction mixture from the reaction with lithium bromide and triethylamine in THF showed it to comprise a 25:1:1:1 mixture of (22a), (23a), (24) and (25) respectively.[19] Trituration of the crude solid with ether-hexane afforded (22a) (85%) which crystallized from ether as colourless rods, m.p. 119-121°C (lit.[19] 122-123°C), 7.9-6.8 (m, 20H, ArH), 4.6 (d, 1H, J 9.2Hz, 5-H), 4.42 (d, 1H, J 8.5Hz, 3-H), 3.85 (t, 1H, 4-H) and 3.72 (s, 3H, OMe). (b) The reaction was repeated in acetonitrile using silver acetate and triethylamine (Table 3). Work-up afforded a yellow gum whose p.m.r. spectrum showed it to comprise a 4:3:1 mixture of (22a), (25) and (23a) respectively. Trituration with ether-hexane afforded the mixed isomers (95%) as a colourless solid.

Methyl 2-methyl-c-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (9b, R=H). Obtained in 59 (AgOAc) and 55(LiBr)% yield as colourless prisms from dichloromethane-ether, m.p. 220-222°C (lit.[17] m.p. 220-222°C).

Dimethyl 2-methyl-c-5-phenyl-r-2,c-4-pyrrolidine dicarboxylate (21b). Obtained as a colourless oil (lit.[1] m.p. 26-28°C) whose spectral data were identical to that reported previously.[1]

Dimethyl N-benzylideneglutamate (26). Benzyltrimethylammonium methoxide (BTAM) (450mg of a 40% w/w solution in methanol, 0.1mmol) were added to a stirred solution

of methyl N-benzylidenealaninate (1.92g, 1.0mmol) and methyl acrylate (860mg, 1.0mmol) in benzene (25ml) at room temperature. The mixture was stirred at room temperature for 24h. and then water (200ml) added. The aqueous layer was separated and extracted with ether (2 x 100ml) and the combined organic layers dried ($MgSO_4$) and the solvent removed to leave a pale yellow oil. Distillation of the oil afforded the product (2.55g, 92%) as a colourless viscous oil, b.p. 155-157°C/1.5mmHg (Found: C, 65.15; H, 7.15; N, 5.65. $C_{15}H_{19}NO_4$ requires C, 64.95; H, 6.90; N, 5.05%); δ 8.3 (s, 1H, CH=N), 7.8-7.4 (m, 5H, ArH), 3.75 and 3.7 (2 x s, 2 x 3H, OMe), 2.45 (m, 4H, CH_2CH_2) and 1.5 (s, 3H, Me); m/z(%) 277 (M^+, 0.5), 262(2), 246(6) and 218(100).

Trimethyl 2-methyl-c-5-phenylpyrrolidine-r-2,t-3,c-4-tricarboxylate (23b) and trimethyl 2-methyl-c-5-phenylpyrrolidine-r-2,c-3,t-4-tricarboxylate (22b).

(23b) The product crystallized from ether-petroleum ether as colourless prisms, m.p. 101-103°C (Found: C, 60.60; H, 6.55; N, 4.20. $C_{17}H_{21}NO_6$ requires C, 60.90; H, 6.30; N, 4.20%); δ 7.3 (m, 5H, ArH), 4.82 (d, 1H, J 9.3Hz, 4-H), 4.0 (d, 1H, J 9.3Hz, 1-H), 3.86 (s + overlapping t, 4H, OMe and 5-H), 3.72 and 3.17 (2 x s, 2 x 3H, OMe), 2.8 (br s, 1H, NH) and 1.4 (s, 3H, Me); m/z(%) 335 (M^+, 4), 276(87), 216(100), 191(54), 184(38), 177(71), 158(22), 157(18) and 131(70).

(22b) Obtained as colourless prisms from ether-petroleum ether, m.p. 79-81°C (lit.[19] 78-81°C). The product was identical to that described previously.[19]

Methyl c-4(2-naphthyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (9c). Obtained as colourless rods from methanol, m.p. 210-212°C (Found: C, 72.20; H, 5.35; N, 6.95. $C_{24}H_{20}N_2O_4$ requires C, 72.00; H, 5.05; N, 7.00%); δ ($CDCl_3$ + 1 drop D_2O) 7.9-7.11 (m, 12H, ArH), 4.75 (d, 1H, J 8.6Hz, 4-H), 4.18 (d, 1H, J 6.45Hz, 2-H), 3.92 (s, 3H, OMe), 3.78 (dd, 1H, J 7.8 and 6.5Hz, 1-H) and 3.66 (t, 1H, J 8.5 and 7.8Hz, 5-H); m/z(%) 400 (M^+, 11), 266(11), 227(76), 196(13), 194(14), 168(100) and 141(86)

Dimethyl c-5(2-naphthyl)-r-2,c-4-pyrrolidine dicarboxylate (21c). Obtained by preparative t.l.c. as a thick colourless oil (Found: C, 68.40; H, 6.30; N, 4.60. $C_{18}H_{19}NO_4$ requires C, 69.00; , 6.10; N, 4.50%); δ 7.8-7.39 (m, 7H, ArH), 4.68 (d, 1H, J 7.65Hz, 5-H), 4.06 (t, 1H, J 8.2Hz, 2-H), 3.84 (s, 3H, OMe), 3.38 (dd, 1H, 4-H), 3.12 (s, 3H, OMe), 2.52 (br s, 1H, NH) and 2.47 (t, 2H, 2 x H-3); m/z(%) 313 (M^+, 57), 255(11), 254(63), 227(81), 196(31), 194(33) and 167(100).

N.m.r. experiments Methyl 2-naphthylideneglycinate (18mg, 8.0 x 10^{-5}mol), and silver acetate (20mg, 1.2 x 10^{-4}mol) or lithium bromide (10.5mg, 1.2 x 10^{-4}mol) were weighed into a dry n.m.r. tube. Methyl acrylate (13.7mg, 1.6 x 10^{-4}mol) dissolved in the appropriate deuteriated solvent (0.5ml) was then added followed by a solution of triethylamine (8mg, 8.0 x 10^{-5}mol) in the same deuteriated solvent (0.5ml). The p.m.r. spectrum of the mixture was then determined at intervals. Substantial amounts of the silver acetate remained undissolved whilst the lithium bromide dissolved completely. Using silver acetate the approximate time for complete reaction was 10 min.(DMSO), 30 min. (acetonitrile) and 35 min.(DMF). A larger scale reaction in N-methylacetamide as solvent was analysed by removal of aliquots at 5 min. intervals and this reaction was complete in less than 10 min. Using lithium bromide in DMSO no reaction was observed after 0.5h.

Epimerisation Studies A mixture of dimethyl c-5(2-naphthyl)-r-2, c-4-pyrrolidine dicarboxylate (21c) (25mg, 8.0 x 10^{-5}mol), silver acetate (20mg, 1.2 x 10^{-4}mol), and triethylamine (8mg, 8.0 x 10^{-5}mol) in the appropriate deuteriated solvent (acetonitrile, toluene) was maintained at room temperature (CD_3CN, 10h) or 110°C (C_7D_8, 10h). No change was observed in CD_3CN spectrum whilst the spectrum in C_7D_8 showed slow formation of second isomer after 7h at 110°C.

Dimethyl 2-(2-naphthyl)-8-oxo-azabicyclo[3.3.0]octane-3,5-dicarboxylate (28). The product was separated by preparative t.l.c. eluting with 1:1 v/v ether-petroleum ether and it crystallised from ether-petroleum ether as colourless needles, m.p. 45-47°C; m/z M^+ 367.1419, $C_{21}H_{21}NO_5$ requires 367.1418; δ 7.87 (s, 1H, ArH), 7.82-7.38 (m, 6H, ArH), 5.50 (d, 1H, J 8.65Hz, 2-H), 3.86 (s, 3H, OMe), 3.74 (m, 1H, 3-H), 3.0 (s, 3H, OMe), 3.1-2.93 (m, 2H, 7-H), and 2.35 (m, 4H, CH_2 and CH_2CO); δ (^{13}C) 177.1, 174.0 and 171.7 (amide and ester carbonyl carbon atoms); m/z(%) 367 (M^+, 8), 308(15), 170(100), 110(33) and 84(55).

Trimethyl c-5(2-naphthyl)pyrrolidine-r-2,t-3,c-4-tricarboxylate (23c) and trimethyl c-5(2-naphthyl)pyrrolidine-r-2, c-3, t-4-tricarboxylate (22c).

(23c) Obtained as colourless rods from ether-petroleum ether, m.p. 93-94°C (Found: C, 64.70; H, 5.90; N, 3.85. $C_{20}H_{21}NO_6$ requires C, 64.70; H, 5.70;

N, 3.75%); δ 7.8-7.26 (m, 7H, ArH), 4.80 (d, 1H, J 9.65Hz, 5-H), 4.28 (d, 1H, J 7.3Hz, 2-H), 3.85 and 3.77 (2 x s, 2 x 3H, OMe), 3.67 (m, 2H,3-H and 4-H) and 3.08 (s, 3H,OMe); m/z(%) 313 (M^+, 57), 254(63), 227(81), 196(31), 195(14), 194(23), 167(100) and 86(30).

(22c) This minor isomer was obtained as a colourless gum by preparative t.l.c.; m/z M^+ 371.1366, $C_{20}H_{21}NO_6$ requires 371.1368; δ 7.8-7.46 (m, 7H, ArH), 4.50 (d, 1H, J 9.0Hz, 5-H), 4.28 (d, 1H, J 8.5Hz, 2-H), 3.79 (dd, 1H), 3.78, 3.72 and 3.63 (3 x s, 3 x 3H, OMe) and 3.52 (dd, 1H); m/z(%) 371 (M^+, 53), 312(13), 280(29), 227(100), 167(81) and 83(40).

2,3-Di(methoxycarbonyl)-2-methyl-4H-2,3,3a,9b-tetrahydropyrro[2,3-d]benzo[b]pyran (34a). Prepared from methyl N-[2-(3-carbomethoxyprop-2-enyl)oxy] benzylidenealaninate (1.36g, 5mmol), silver acetate (1.25g, 7.5mmol), and triethylamine (0.5g, 5mmol) in acetonitrile (20ml) according to the general procedure. The product (1.0g, 80%) crystallised from ether-petroleum ether as colourless needles, m.p. 131-133°C (Found: C, 62.85; H, 6.30; N, 4.05. $C_{16}H_{19}NO_5$ requires C, 62.95; H, 6.25; N, 4.60%); δ ($CDCl_3$ + 1 drop D_2O) 7.27-6.8 (m, 4H, ArH), 4.56 (dd, 1H, CHO), 4.13 (t, 1H, CHO), 3.90 (d, 1H, J 10.7Hz, CHN), 3.70 and 3.69 (2 x s, 2 x 3H, OMe), 2.65 (d, 1H, J 12Hz, C<u>H</u>CO_2Me), 2.5 (m, 1H) and 1.7 (s, 3H, Me); m/z(%) 305 (M^+, 20), 304(14), 246(100), 214(16), 187(15), 145(29), 128(49), 68(22) and 43(41).

2,3-Di(methoxycarbonyl)-2-phenyl-4H-2,3,3a,9b-tetrahydropyrro[2,3-d]benzo[b]pyran (34b). Prepared in analogous way to the above but with a 10h reaction time. The product (88%) crystallised from ethanol as colourless rods, m.p. 143-146° (lit.[20] 146-147°C); δ 7.9-7.14 (m, 9H, ArH), 4.49 and 4.0 (2 x dd, 2 x 1H, CH_2O), 3.81 and 3.63 (2 x s, 2 x 3H, OMe), 3.24 (d, 1H, J 11.6Hz, C<u>H</u>CO_2Me), and 2.58 (m, 1H, C<u>H</u>CH_2O). The signal for the CHN proton is obscured by the OMe signal at 3.63. A small amount (ca 10%) of a second product was detected. It did not appear to be a stereoisomer of (34b) as was not studied further.

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