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Prototropic Routes to 1,3- and 1,5-Dipoles, and 1,2-Ylides: Applications to the Synthesis of Heterocyclic Compounds

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1 Introduction

Proton transfer processes are of fundamental importance in synthetic and mechanistic chemistry, and in biological systems based, as they are, on an aqueous (protic) environment.[1] Formal intramolecular proton transfers can be divided into two broad classes. The first class comprises unassisted or concerted hydrogen migrations where the migrating hydrogen moves intramolecularly over a π-electron framework under thermal or photochemical activation, *e.g.* (1 ⇌ 2).[2] The electronic requirements and stereochemical outcome of this type of migration (sigmatropic reactions) were delineated by Woodward and Hoffmann in their classic series of papers on orbital symmetry controlled reactions[3] and have been confirmed by many subsequent studies.[4] The second class comprises proton transfers where the assistance of an acid, base, transition metal, or transition-

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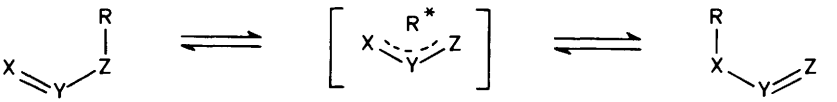
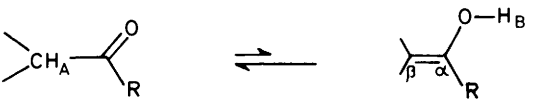


Scheme 1



(3) (4)

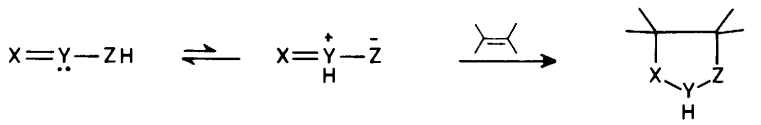
[1] R. P. Bell, 'The Proton in Chemistry', Cornell University Press, New York, 2nd edn., 1973; R. Stewart, 'The Proton: Applications to Organic Chemistry', Academic Press, 1985.
[2] R. M. Duhaime and A. C. Weedon, *J. Am. Chem. Soc.*, 1985, **107**, 6723.
[3] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Verlag Chemie, Weinheim, Germany, 1970.
[4] C. W. Spengler, *Chem. Rev.*, 1976, **76**, 187.

metal complex is required. In this type of reaction the intramolecularity of the proton transfer can vary from zero to 100%. It is this class that our research is concerned with.

2 Prototropy in the Four-atom X=Y–ZH System

Tautomerism is a term applied to reversible isomeric changes involving heterolysis and subsequent recombination of the ions to give an isomer of the original compound (Scheme 1).[5] Thus R* in Scheme 1 could carry either a positive or negative charge with the X–Y–Z framework carrying the opposite charge. When R = H^+ (Scheme 1) the tautomeric process is called prototropy.[5] Prototropy in the four-atom X=Y–ZH system includes some of the most important processes in organic chemistry such as keto–enol [(3) $\rightleftharpoons$ (4)],[6] imine–enamine,[7] hydrazo–azo,[8] oxime–nitroso,[9] and nitro–*aci*-nitro[10] equilibria, and alkene isomerization.[11] All these processes have attracted substantial mechanistic studies and all are important in organic synthesis. Keto–enol equilibration is the most important of this group and is the basis of the aldol condensation, Claisen ester condensation, Michael addition reaction, Robinson ring annulation *etc.* These synthetic applications owe their existence to the dramatic difference in chemical reactivity of the two tautomeric forms (3) and (4). Thus the labile proton H_A in (3) has a pk_a of *ca.* 19, whilst H_B in (4) has a pk_a of *ca.* 10. The diagnostic chemical reactivity of (3) is nucleophilic attack at the carbonyl group, whilst that of (4) is electrophilic attack at the β-carbon atom. In simple ketones the concentration of enol is extremely small (*e.g.* for acetone the equilibrium constant $K = \frac{[\text{enol}]}{[\text{ketone}]} = 6.0 \times 10^{-8}$)[12] and such enols cannot be detected even by sensitive modern spectroscopic techniques. Detection and quantitation is based on the specific chemistry of the enol allied to kinetic studies, *e.g.* Lapworth's early kinetic studies[13] providing the first clear evidence for the intervention of an enol in the bromination of methyl ketones. Of course stable enols are known in which special substituents are employed to impart enhanced stability to the enol form.[14] Recently unstable enols have been generated and detected spectroscopically under carefully controlled conditions (*e.g.* propionaldehyde enols from enol ether precursors)[15] or by flash vacuum pyrolysis.[16]

[5] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', G. Bell and Sons, London, 1953.
[6] S. Forsen and M. Nilsson, in 'The Chemistry of the Carbonyl Group', Vol. 2, ed. J. Zabicky, Wiley, 1970, p. 157.
[7] C.-G. Shin, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 1657.
[8] P. Griess, *Ber.*, 1874, **7**, 1618; *Annalen*, 1886, **137**, 60.
[9] W. A. Tilden and W. A. Shenstone, *J. Chem. Soc.*, 1877, **31**, 554; R. Pummerer and F. Graser, *Annalen*, 1953, **583**, 207.
[10] D. Turnbull and S. M. Maron, *J. Am. Chem. Soc.*, 1943, **65**, 212.
[11] H. H. Niemeyer and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 1974, 799; S.-Y. Yokoyama, K.-I. Tanaka, and H. Haneda, *ibid.*, 1982, 820.
[12] J. P. Guthrie, *Can. J. Chem.*, 1979, **57**, 797.
[13] A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 40.
[14] H. Hart, *Chem. Rev.*, 1979, **79**, 515.
[15] B. Capon and A. K. Siddhauta, *J. Org. Chem.*, 1984, **49**, 255.
[16] J.-L. Ripoll and M.-C. Lasne, *Tetrahedron Lett.*, 1980, 463; M.-C. Lasne and J.-L. Ripoll, *ibid.*, 1982, 1587; A. Hakiki and J.-L. Ripoll, *Tetrahedron Lett.*, 1984, 3459; S. Saito, *Chem. Phys. Lett.*, 1976, **42**, 399.



(5) (6) (7)

Type				*No. of lone pair atoms*	*Examples*
I	X=Y–ZH			0	Alkenes
II	$\ddot{X}$=Y–ZH	X=$\ddot{Y}$–ZH	X=Y–$\ddot{Z}$H	1	Imines, ketones, nitroalkanes
III	$\ddot{X}$=$\ddot{Y}$–ZH	$\ddot{X}$=Y–$\ddot{Z}$H		2	Hydrazones, oximes, amidines
IV	$\ddot{X}$=$\ddot{Y}$–$\ddot{Z}$H			3	Triazenes

Scheme 2

X=Y–ZH Systems can be divided into four classes (Scheme 2) depending on the number of constituent atoms that possess lone pairs of electrons (note that more than one pair may be located on each atom). Formal 1,3-H shifts from Z to X (Scheme 1, R = H) are normally achieved by the intervention of a suitable catalyst although isotope labelling studies show these catalysed prototropic equilibria often involve a substantial intramolecular component. Thus in base-catalysed alkene isomerizations, a type I system (Scheme 2), greater than 90% intramolecularity has been observed,[11,17] whilst in imines, a type II system, up to *ca.* 50% intromolecularity has been reported.[18] The stereoselectivity and intramolecularity of the latter type of isomerizations have attracted attention[19] because of their relationship to the biochemical transformations of α-amino acids catalysed by pyridoxal enzymes. These enzymic isomerizations involve a suprafacial 1,3-proton transfer in pyridoxal-amino acid imines.[20] The precise mode of association between the protonated base and the allyl- or azaallyl-anion leading to intramolecular 1,3-proton transfer is unclear. The X=Y–ZH system may act as its own catalyst for a formal 1,3-H shift. Thus triazene isomerizations ($R^1N{=}N{-}NHR^2 \rightleftharpoons R^1NH{-}N{=}NR^2$) are usually bimolecular although a radical mechanism may be dominant in some cases.[21]

Thermal concerted 1,3-H shifts in X=Y–ZH systems would, if observed, occur *via* an *antarafacial* migration (4π-electron transition state)[3] with ψ_2 the dominant molecular orbital (Figure 1). The migrating hydrogen is required to transfer from the top face of the π-system to the bottom face during its 1,3-shift. The geometrical constraints imposed by the three-atom framework and the availability of only an *s*

[17] J. Klein and S. Brenner, *Chem. Commun.*, 1969, 1020; S. Bank, C. A. Rowe, and A. Schriesheim, *J. Am. Chem. Soc.*, 1963, **85**, 2115.
[18] R. D. Guthrie and J. L. Hedrick, *J. Am. Chem. Soc.*, 1973, **95**, 1971.
[19] D. A. Jaeger, M. D. Broadhurst, and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 717.
[20] J. C. Vederas and H. G. Floss, *Acc. Chem. Res.*, 1980, **13**, 455.
[21] K. Vaughan, *J. Chem. Soc., Perkin Trans. 2*, 1977, 17; L. Lunazzi, G. Panciera, and M. Guerra, *ibid.*, 1980, 52.

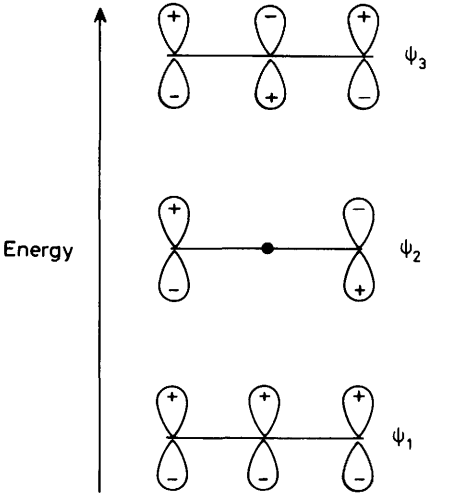
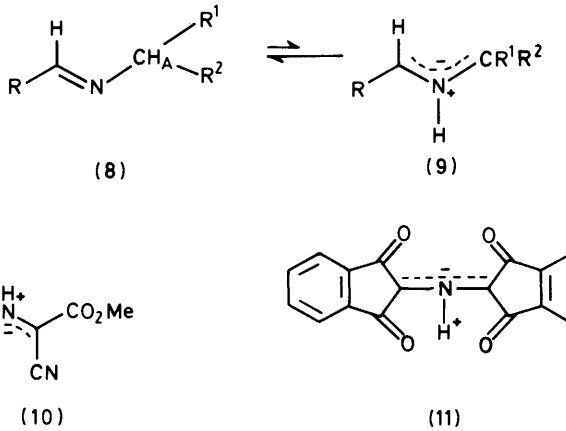


Figure 1 *Molecular orbitals of the allyl system* (X, Y, *and* Z=C)



orbital on the migrating H-atom conspire to make the thermal *antarafacial* process unrealizable. However, there is no orbital symmetry restraint on step-wise processes for achieving the 1,3-proton transfer. Our contributions to this area of chemistry began with the realization that when the central Y atom in an X=Y–ZH system possesses a lone pair of electrons (Scheme 2, types II–IV) a formal 1,2-H shift [(5) ⇌ (6)] becomes possible. A concerted 1,2-H shift involving the electrons of XY double bond and a 1,3-charge separation involves unfavourable orbital interactions and prohibitively high energies,[22] *e.g.* reference to Figure 1 shows a

[22] P. D. Adeney, W. J. Bouma, L. Radour, and W. R. Rodwell, *J. Am. Chem. Soc.*, 1980, **102**, 4069; see also Y. Yoshioka and H. F. Schaefer, *ibid.*, 1981, **103**, 7366 for the effect of orbital population on 1,2-H shifts.

node at Y in the dominant molecular orbital (ψ_2) in such processes, although when Y = C there is a small coefficient at Y.[23] The lone pair on Y in (5) is orthogonal to the XY π-system and thus concerted proton transfer from Z to this orthogonal lone pair is free of orbital symmetry restrictions. However, a stepwise proton transfer would intuitively seem more likely. These considerations led us to suggest that such a new and novel type of prototropy, 1,2-proton shifts [(5) $\rightleftharpoons$ (6)], should occur resulting in a general method for generating certain 1,3-dipolar species (6). Like the keto–enol situation discussed earlier the 1,3-dipole (6) would be expected to exhibit markedly different chemical properties to (5) and to be present in very small concentrations. Thus detection of (6) would require kinetic studies and/or a chemical test specific for (6). Fortunately, in the case of 1,3-dipoles a simple and synthetically useful method of detection is available, the 1,3-dipolar cycloaddition reaction (6) ⟶ (7). This is the most versatile method available for the synthesis of 5-membered heterocycles.[24]

The generality and scope of this remarkable reaction were first recognized by Huisgen.[25] To date we have evidence for dipole formation in three X=Y–ZH systems representing types II and III (Scheme 2). These are: imines (C=N–CH), oximes (C=NOH), and hydrazones (C=N–NH). We have developed a wide range of simple, synthetically useful reactions based on thermal generation of dipoles from these and other sytems.

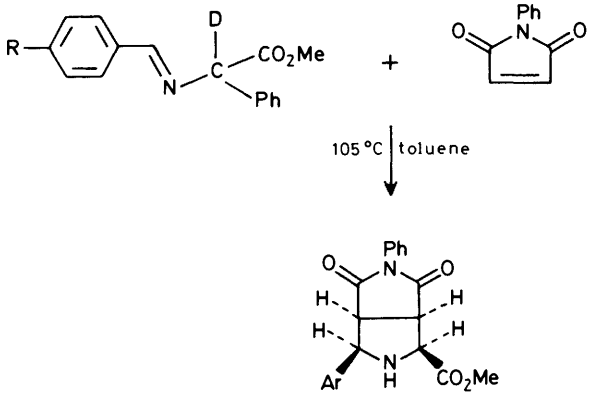
Imines.—These are type II X=Y–ZH systems and the formal 1,2-H shift in imines [(8) $\rightleftharpoons$ (9)] results in azomethine ylides with an NH group. Such species are rare and to date only two stable examples (10)[26] and (11)[27] are known. Compound (11) is of interest since it is the protonated form of Ruhemann's purple, the product of the ninhydrin test. We have shown[27] that several types of azomethine ylide are involved in this useful test for α-amino acids, which incidentally, also forms the basis of the method for detecting latent fingerprints on paper and other suitable materials.

The facility with which the azomethine ylide (9) is formed would be expected to be dependent on the basicity of the central nitrogen atom and on the pK_a of the proton H_A in (8). These properties will, in turn, be influenced by the nature of the substituents R, R^1, and R^2. The effect of imine basicity on rate of dipole generation is illustrated in Figure 2.[28] Note that dipole formation is rate determining when *N*-phenylmaleimide is the dipolarophile.

The basicity of the central nitrogen atom falls from R = NMe_2 (the most basic) to R = NO_2 due to the mesomeric effects of these substituents (13) and (14), relayed through the benzene ring. Thus the variation in rate, although not large, is

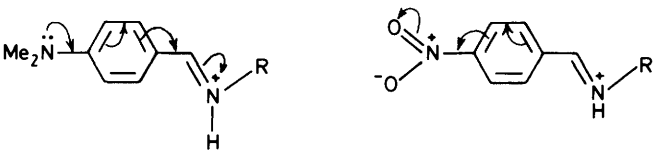
[23] K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287.
[24] R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403; A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123; W. Oppolzer, *ibid.*, 1977, **16**, 10.
[25] R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565 and 633.
[26] J.-P. Fleury, J.-P. Schoeni, D. Cleriu, and H. Fritz, *Helv. Chim. Acta*, 1975, **58**, 2018.
[27] R. Grigg, J. F. Malone, T. Mongkolaussavaratana, and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1986, 421.
[28] R. Grigg, H. Q. N. Gunaratne, and J. Kemp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 41.

in the expected direction. The deuterium isotope effect (Figure 2) is comparatively small for a process involving rate-determining dipole formation and the reason for this is uncertain at present.



	Rate Constant (s^{-1})	*Isotope Effect*
NMe_2	44.6×10^{-5}	1.21
MeO	7.8×10^{-5}	2.14
H	3.55×10^{-5}	2.70
CN	0.72×10^{-5}	2.75
NO_2	0.80×10^{-5}	2.17

Figure 2 *The effect of imine basicity on rate of dipole generation*

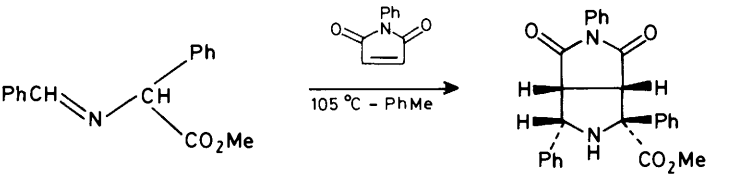


Stabilizing (13)

Destabilizing (14)

The formation of 1,3-dipoles from neutral imines is catalysed by both Brönsted (Figure 3) and Lewis (Figure 4) acids.[29] The catalysed cycloadditions are both stereo- and regio-specific and with Brönsted acid catalysts the rate increases with decreasing pk_a of the catalyst. In both catalysed and uncatalysed cycloadditions, imines of optically active α-amino acid esters give racemic cycloadducts. It is apparent from Figures 2—4 that dipole formation is stereospecific in both the catalysed and uncatalysed reactions and that the cycloadditions involve an *endo* transition state (Figure 2 and 3). Thus some property inherent in the imine system

[29] R. Grigg and H. Q. N. Gunaratne, *J. Chem. Soc., Chem. Commun.*, 1982, 384.

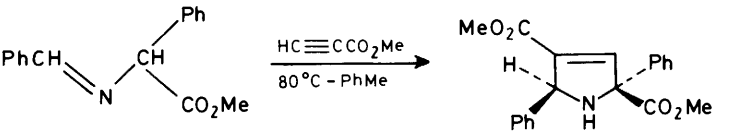


Catalyst (1 mole)	pk_a	$t_{\frac{1}{2}}$ (min)
None	—	120 ± 4
2-Pyridone	11.99	88 ± 6
Meldrums acid[a]	5.5	5[b]
$MeCO_2H$	4.75	6[b]
2,4-Dinitrophenol	4.0	3[b]

[a] 2,2-Dimethyl-1,3-dioxan-4,6-dione. [b] Approximate values

Figure 3

imparts a kinetic bias to one dipole. The simplest explanation of this observation is shown in Scheme 3, and involves an intermediate hydrogen-bonded enol (uncatalysed route) or a hydrogen-bonded protonated imine (acid-catalysed route). We have shown that the same dipole configuration is generated in the racemization of α-amino *acids* in the presence of aldehydes.[30]

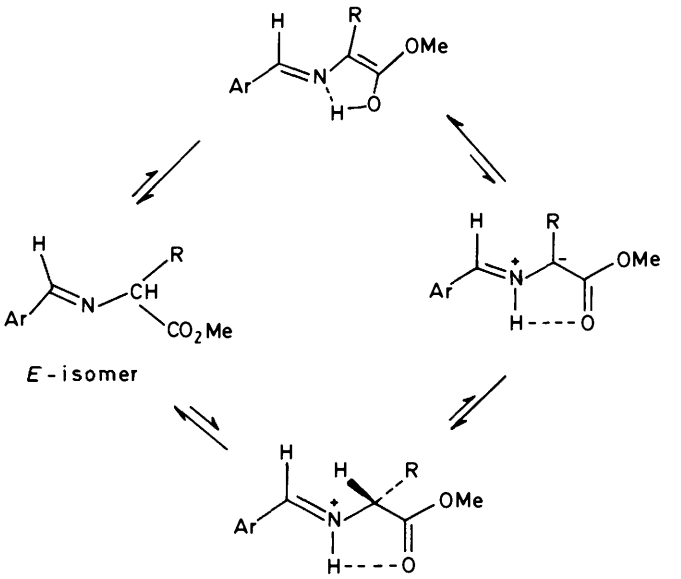


Lewis Acid	$t_{\frac{1}{2}}$ (h)	*Yield* (%)
—	38	94
$MeCO_2H$	1.8	—
$Zn(OAc)_2.2H_2O$	3	88
AgOAc	3.25	95
$LiOAc.2H_2O$	5.5	93

Figure 4

The formation of azomethine ylides by prototropy from imines tolerates a range of aromatic, heterocyclic, and aliphatic aldehydes as imine precursors although the opportunity for imine–enamine equilibration and subsequent side-reactions of the enamine tautomer frequently makes aliphatic aldehydes less attractive. Other groups can replace ester for the activation of the ZH proton provided they lower

[30] R. Grigg and H. Q. N. Gunaratne, *Tetrahedron Lett.*, 1983, **24**, 4457; K. Amornraksa, R. Grigg, H. Q. N. Gunaratne, J. Kemp, and V. Sridharan, *J. Chem. Soc., Perkin Trans. 1*, in press.



Scheme 3

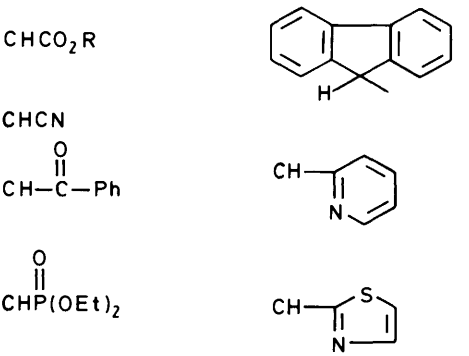


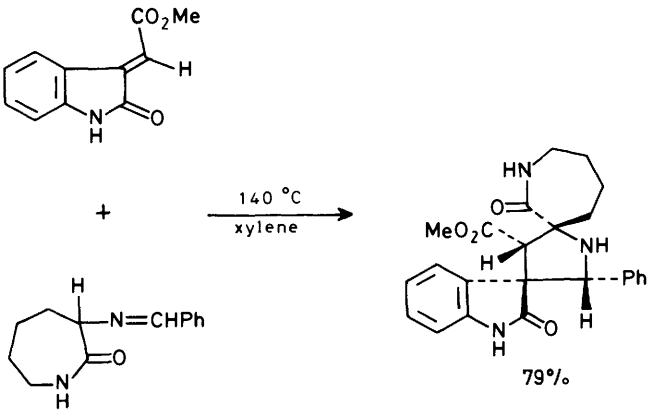
Figure 5 *Groups activating the* ZH *proton*

the pK_a of the ZH proton sufficiently to permit prototropy and some of those studied are listed in Figure 5. We have developed all these activating groups[31] apart from cyano which has been studied by others.[32]

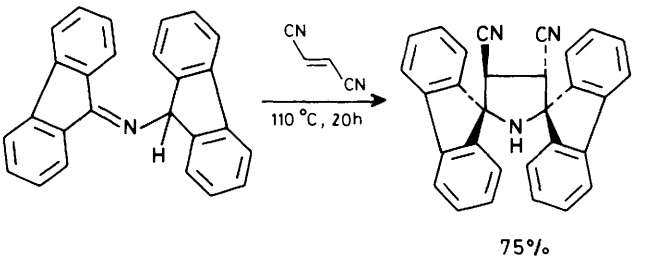
The prototropically generated azomethine ylides undergo cycloadditions with a

[31] R. Grigg, H. Q. N. Gunaratne, V. Sridharan, and S. Thianpatanagul, *Tetrahedron Lett.*, 1983, **24**, 4363, and unpublished observations.

[32] M. Joucla and J. Hamelin, *Tetrahedron Lett.*, 1978, 2885; O. Tsuge, K. Ueno, S. Kanemasa, and K. Yorozu, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1809.



Scheme 4



Scheme 5

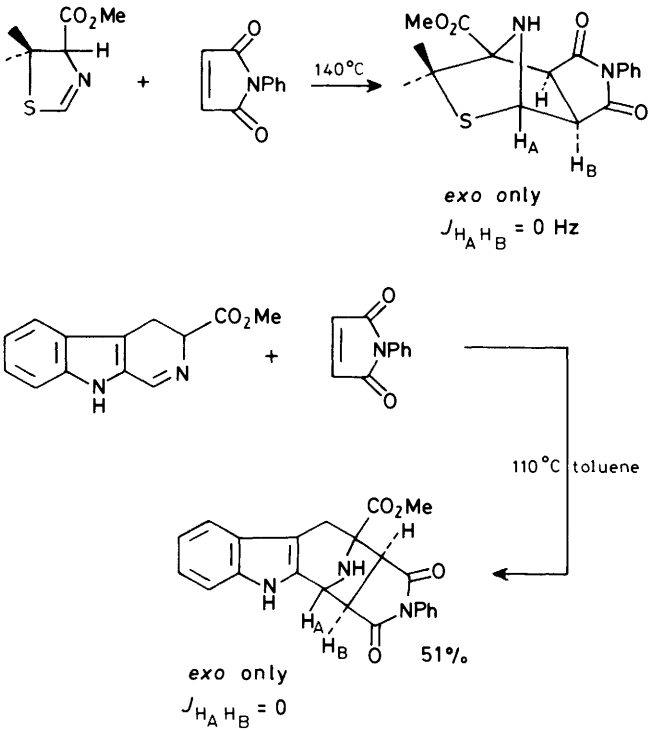
wide range of dipolarophiles, invariably *via endo* transition states, providing many novel heterocyclic compounds from readily available starting materials. Some examples of these simple one-step processes are shown in Schemes 4 and 5.

The reaction can also be applied to the synthesis of bridged ring compounds and two examples of this are shown in Scheme 6.[33]

Pyridoxal (Vitamin B_6) phosphate-dependent enzymes occur widely and are responsible for the synthesis, racemization, degradation, and interconversion of α-amino acids in living systems.[34] These processes are known to proceed *via* formation of the corresponding pyridoxal imines (15). The initial reactive intermediates (16) or (17) are generated by cleavage of either bond (a) or (b) in (15) together with protonation of the pyridine nitrogen atom. Stereoelectronic control

[33] R. Grigg, L. D. Basanagoudar, D. A. Kennedy, J. F. Malone, and S. Thianpatanagul, *Tetrahedron Lett.*, 1982, 2803; R. Grigg and D. Vipond, unpublished observations.

[34] K. Bloch in 'The Enzymes', ed. P. Boyer, Academic Press, 3rd edn., 1972, Vol. 5, p. 441; L. Davis and D. E. Metzler, *ibid.*, p. 33.

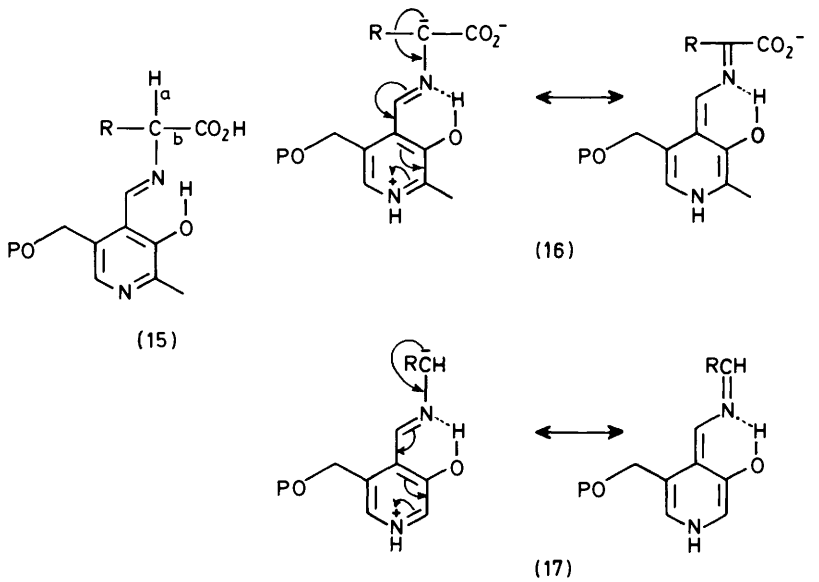


Scheme 6

requires that the breaking bond [bond (a) or bond (b) in (15)] is aligned with the pyridyl azomethine π-system.[35]

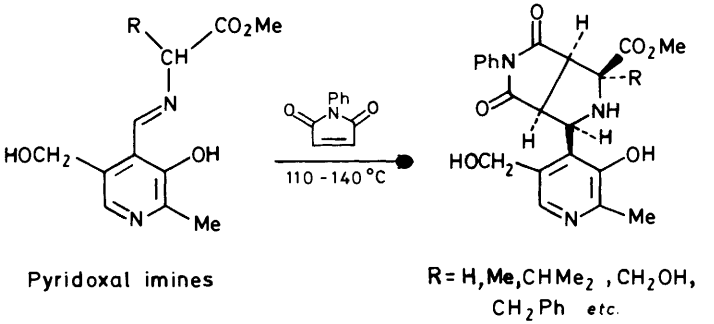
Racemases and transaminases function by cleavage of bond (a) in (15) and led us to consider, in the light of our experience with imines of α-amino acid esters, that (16) might be more properly regarded as 1,3-dipole with a proton residing on the imine nitrogen atom.[36] We therefore prepared a range of pyridoxal imines of α-amino acid esters and examined their suitability as 1,3-dipole precursors. We were rewarded with a series of smooth, stereospecific cycloadditions (Scheme 7) which, with one or two exceptions, occur in excellent yield.[37] Other reactions relevant to pyridoxal enzymes involving cleavage of bond (b) in (15) are discussed later in this

[35] H. C. Dunathan, *Proc. Natl. Acad. Sci. U.S.A.*, 1966, **55**, 712; J. R. Fischer and E. H. Abbot, *J. Am. Chem. Soc.*, 1979, **101**, 2781.
[36] P. Armstrong, D. T. Elmore, R. Grigg, and C. H. Williams, *Biochem. Soc. Trans.*, 1986, 404.
[37] R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1978, 2823; R. Grigg and S. Thianpatanagul, unpublished observations.



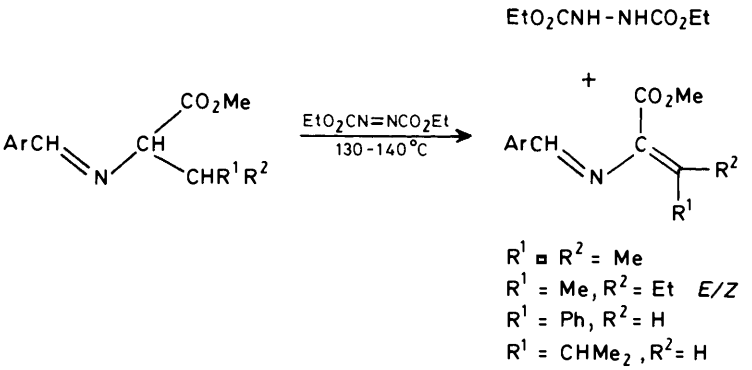
article, but it is clear that the concept of pyridoxal imines functioning as 1,3-dipoles provides a new approach to the design of suicide substrates for pyridoxal enzymes.[36]

An interesting and synthetically useful reaction occurs between imines and azoesters leading to imines of dehydroamino acid esters in good yield (Scheme 8). Several mechanisms can be advanced for this reaction but we accumulated good evidence in favour of Scheme 9 which requires formation of a 1,3-dipole and cycloaddition to give an undetected triazolidine.[38] The key feature of the proposed

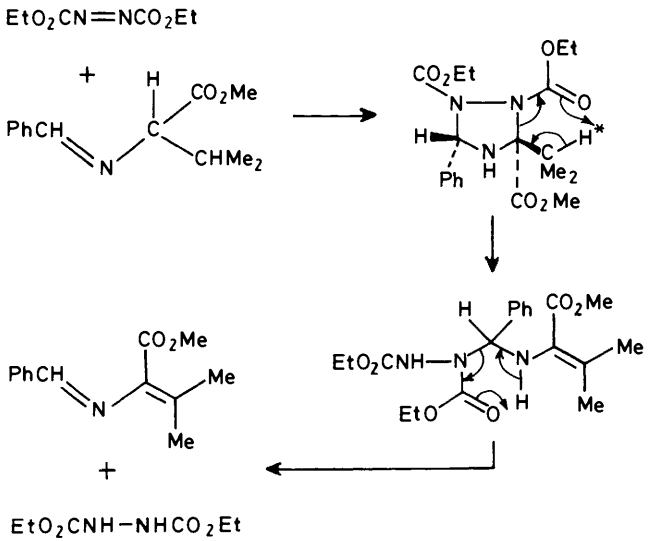


Scheme 7

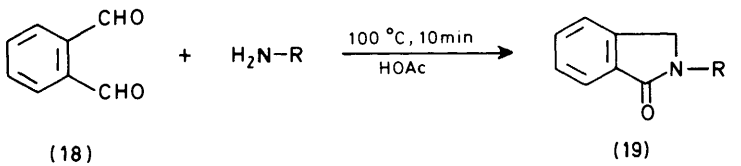
[38] R. Grigg and J. Kemp. *J. Chem. Soc., Chem. Commun.*, 1977. 125.



Scheme 8



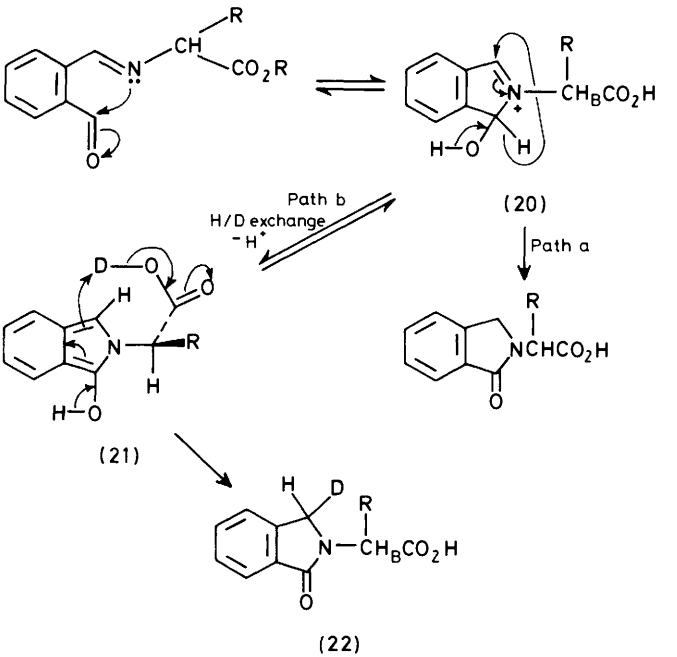
Scheme 9



mechanism is that the intermediate triazolidine is rendered labile by the presence of H*. In accord with this analysis, imines lacking a suitably placed hydrogen atom afford triazolidines in good yield.[38]

In attempting to prepare monoimines of *o*-phthalaldehyde we discovered a new, rapid, simple one-step synthesis of *N*-substituted isoindolin-1-ones (18) ⟶ (19).[39]

A wide variety of amine components (aliphatic, aromatic, heteroaromatic) can be incorporated into (19) and yields are excellent. Two mechanisms were considered



Scheme 10

for this process, which is illustrated for an α-amino acid as the amine component (Scheme 10). First, formation of the monoimine, followed by ring-closure to the carbinolimine (20). Then either a 1,3-hydride shift [Scheme 10, path (a)] in which the hydroxy group aids the 1,3-shift [(20) arrows] or a prototropic pathway [Scheme 10, path (b)]. When the reaction was carried out in deuterioacetic acid, clean incorporation of one deuterium atom into the isoindolin-1-one methylene group was observed. No exchange of H_B was observed, showing that an azomethine ylide was not being generated. Moreover, since the α-amino acid possesses a chiral centre the product from the deuteriation experiment is a mixture of diastereomers.

[39] R. Grigg, H. Q. N. Gunaratne, and V. Sridharan, *J. Chem. Soc., Chem. Commun.*, 1985, 1183.

However, the ratio of the diastereomers was found to be dependent on the steric bulk of the R group in the α-amino acid (Table 1) suggesting the deuteron was delivered intramolecularly [Scheme 10, (21), arrows] to the face of the intermediate isoindole remote from the R group, *i.e.* diastereofacially selective protonation was occurring.[40] Both (*S*)- and (*R*)-amino acids give identical or very similar ratios of diastereomers (Table 1) as expected for intramolecular deuteron transfer *via* (21).

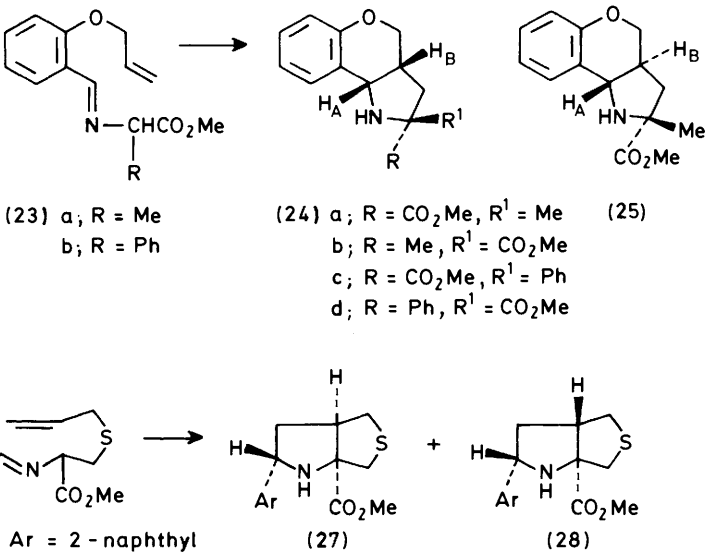


Table 1 *Diastereomer ratios of monodeuterio-*(22)

R in (22)	*Ratio from* (S)-*amino acid*	*Ratio from* (R)-*amino acid*
Me	1:1.20	1:1.18
Ph	1.22:1	1.22:1
$PhCH_2$	1.32:1	1.17:1
$CHMe_2$	1.63:1	2.05:1
CH_2CHMe_2	2.30:1	2.03:1
Bu^t	7.10:1	—

Subsequent to our work some related reactions were reported[41] involving *o*-formylarylazomethylenetriphenylphosphoranes, but without precise mechanistic detail.

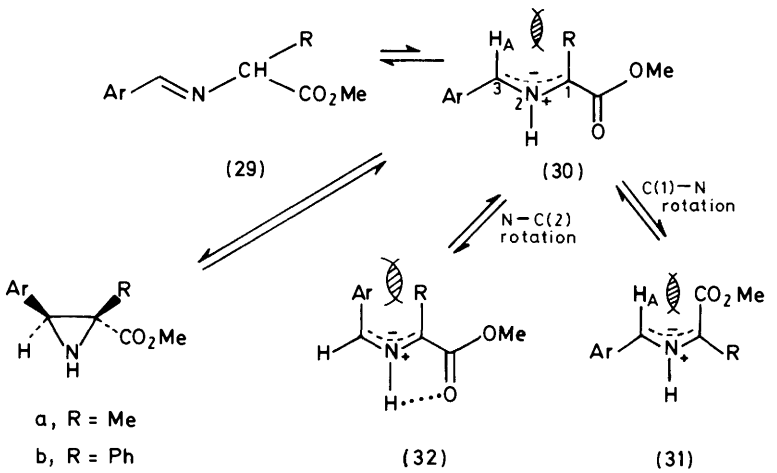
Intramolecular 1,3-dipolar cycloadditions have proved both valuable and powerful in natural product synthesis.[42] Our prototropic generation of azomethine

[40] L. Dunhamel, P. Duhamel, J.-C. Launay, and J.-C. Plaquevent, *Bull. Soc. Chim. France*, 1984, 421.
[41] A. Alemagna, P. del Buttero, E. Licandro, S. Maiovana, and A. Papagni, *Tetrahedron*, 1985, **41**, 3321.
[42] A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123; W. Oppolzer, *ibid.*, 1977, **16**, 10.

ylides from imines provides a simple and effective route to such processes.[43] In intramolecular cycloadditions of imines of α-amino acid esters the dipolarophile can be incorporated into either of the two imine precursors, the aldehyde or the amino-acid esters. Examples of both types have been studied and successful, high yield, cycloadditions achieved in both cases. In every case the major product has *cis*-stereochemistry at the newly created ring junction (*X*-ray crystallography or n.O.e. difference spectroscopy) with zero or $<10\%$ of *trans*-isomer being formed. An example in which the dipolarophile is incorporated into the aldehyde precursor is shown in (23). Heating imine (23a) in xylene (140 °C, 24 h) gives a quantitative yield of an 87:9:4 mixture of (24a), (25), and (24b).[43]

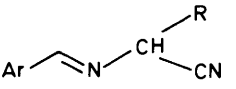
An example in which the dipolarophile is incorporated into the amino acid moiety is provided by (26) which cyclizes (xylene, 140 °C, 24 h) in quantitative yield to a 92:8 mixture of (27) and (28).[43] Cycloadducts (24a), (25), (27), and (28) arise from the 1,3-dipole (30a) which is generated in a kinetically controlled process. The minor product (24b) from (23a) arises from a small amount of dipole (31a) generated by stereomutation of (30a). In contrast to (23a) the imine (23b) gives a *ca.* 50:50 mixture of (24c) and (24d), *i.e.* substantial dipole stereomutation (30b) $\rightleftharpoons$ (31b) occurs (Scheme 11).

Factors Affecting Dipole Stereomutation. The occurrence of dipole stereomutation (30) $\rightleftharpoons$ (31) is a function of both imine structure and dipolarophile reactivity. With unactivated dipolarophiles, (*i.e.* terminal alkenes with no electron-withdrawing substituents) the kinetic dipole (30a) undergoes minor stereomutation [$<5\%$ of (31a) formed][43] whilst with activated dipolarophiles (*e.g.* acrylate, maleate and fumarate esters, *N*-phenylmaleimide *etc.*) no stereomutation is

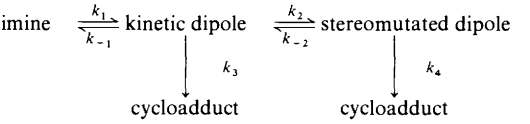


Scheme 11

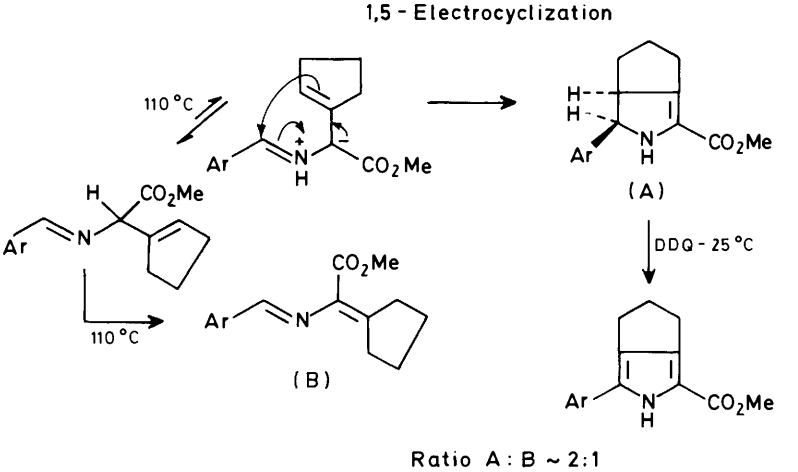
[43] P. Armstrong, R. Grigg, M. W. Jordan, and J. F. Malone, *Tetrahedron*, 1985, **41**, 3547; P. Armstrong and R. Grigg, unpublished observations



(33)



Scheme 12



Scheme 13

observed.[44] In contrast (30b) undergoes essentially complete equilibration with (31b) when generated in the presence of unactivated dipolarophiles,[43] partial equilibration when generated in the presence of maleate and fumarate esters,[44] but does not equilibrate when generated in the presence of maleimides.[45] Thus equilibration of (30) is promoted by the presence of two aryl groups at the termini of the azomethine ylide system (30b). These participate in charge delocalization and lower the C(1)–N(2)–C(3) bond order and hence lower the barrier to dipole stereomutation (Scheme 11).

The stereochemical outcome of the cycloaddition thus depends on the relative rates of cycloaddition (k_3, k_4) and stereomutation (k_2) (Scheme 12). With maleimides as dipolarophiles, dipole formation is rate-determining (cycloaddition

[44] R. Grigg, J. Kemp, and W. J. Warnock, *J. Chem. Soc., Perkin Trans. 1*, in press; R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1980, 2461.

[45] K. Amornraksa, R. Grigg, H. Q. N. Gunaratne, J. Kemp, and V. Sridharan, *J. Chem. Soc., Perkin Trans. 1*, in press.

is fast) and only the kinetic dipole (30) is trapped (Scheme 12, $k_3 \gg k_1$). With less active or unactivated dipolarophiles cycloaddition becomes rate-determining (Scheme 12, $k_1 > k_3$) and stereomutation (30) $\rightleftharpoons$ (31) may compete if the energy barrier to rotation is sufficiently low. Two terminal aryl substituents (30b) are sufficient for this purpose. Studies of the stereochemistry of cycloadducts derived from (29b) and maleate esters[44] support configuration (31b) for the stereomutated dipole rather than (32) (Scheme 11), *i.e.* regiospecific rotation about the C(1)–N(2) bond in (30b) occurs and N(2)–C(3) rotation is not observed. In terms of dipole stability (32) would be predicted to be the least stable of the three azomethine ylides [(30)—(32)] from steric considerations (Ar–R interaction). The relative order of the steric interactions between H_A and R in (30) and H_A and the ester group in (31) will depend on the steric bulk of R. Dipole stereomutation (30) $\rightleftharpoons$ (31) involves loss of *ca.* 5—6 kcal of stabilization due to the intramolecular H-bond in (30). Thus imines lacking a terminal substituent capable of H-bonding might exhibit a lower barrier to dipole stereomutation. In accord with this suggestion the imines (33) are much more susceptible to stereomutation than (29).[46] Based on the extensive studies[47] of the stereomutation of aziridines and the addition of aziridines to dipolarophiles it would be expected that aziridines might feature in the imine–dipole equilibria (Scheme 11). At present we have no evidence for this suggestion.

Further extension of the concept of formal 1,2-H shifts to the generation of 1,*n*-dipoles is conceivable and we have provided an example of 1,5-dipole formation (Scheme 13).[48] The competitive 1,5-electrocyclization leading to A, and double-bond shift leading to B, are solvent-sensitive and the ratio of A to B increases from 2:1 (toluene) to 5.5:1 in acetonitrile.[48]

Speckamp *et al.*[49] have reported an application of this 1,5-electrocyclization to the synthesis of indolines. Our report of a related reaction[50] was subsequently found to be incorrect.[50]

Oximes.—Our initial studies on oximes[51] showed that oximes of aldehydes and ketones give cycloadducts containing two moles of the dipolarophile and that these arise *via* path B of Scheme 14. Oximes are type III X=Y–ZH systems and the presence of two adjacent atoms bearing lone pairs renders them prone to Michael-type additions. To persuade oximes to react by path A (Scheme 14) it is necessary to encourage the formal 1,2-H shift by making available a lower energy pathway. One way of achieving this is by constructing a system that favours an allowed 1,5-H shift and which subsequently permits the possibility of proton transfer by

[46] M. Joucla and J. Hamelin, *Tetrahedron Lett.*, 1978, 2885; O. Tsuge, K. Ueno, S. Kanemasa, and K. Yorozu, *Bull. Chem. Soc. Jpn*, 1986, **59**, 1809.

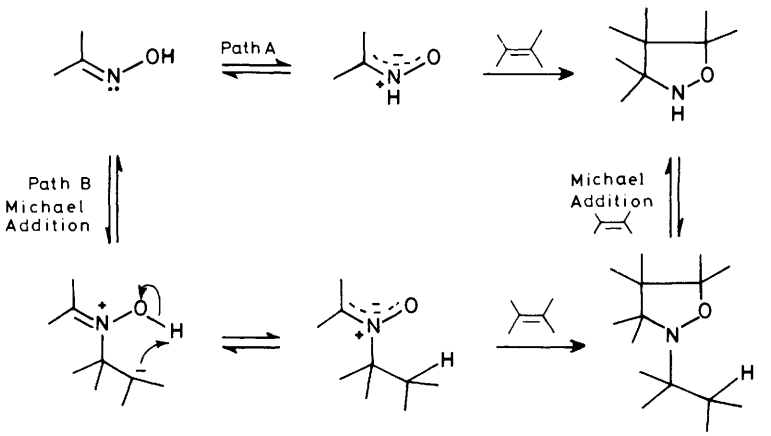
[47] J. W. Lown, *Rec. Chem. Prog.*, 1971, **32**, 51; H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, 1966, **31**, 3924; R. Huisgen, W. Scheer, and H. Mader, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 602 and 604; J. H. Hall and R. Huisgen, *J. Chem. Soc., Chem. Commun.*, 1971, 1187; J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *ibid.*, 1971, 1188; P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, 1970, **35**, 888.

[48] R. Grigg and H. Q. N. Gunaratne, *Tetrahedron Lett.*, 1983, 1201.

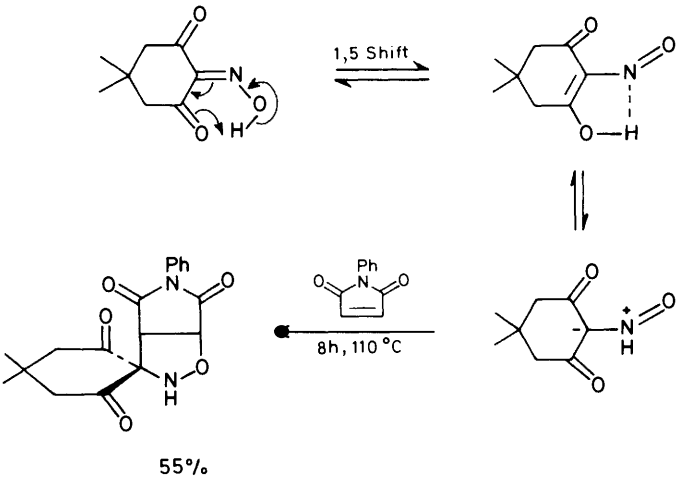
[49] J. Dijink, J. N. Zonjee, B. S. de Jong, and W. N. Speckamp, *Heterocycles*, 1983, **20**, 1255.

[50] R. Grigg and H. Q. N. Gunaratne, *J. Chem. Soc., Chem. Commun.*, 1984, 661; see corrigenda *J. Chem. Soc., Chem. Commun.*, 1985, 1271.

[51] R. Grigg, M. Jordan, A. Tangthongkum, F. W. B. Einstein, and T. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1984, 47.



Scheme 14



Scheme 15

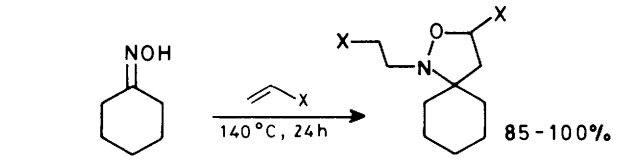
intramolecular hydrogen bonding. The successful realisation of this objective[52] is illustrated in Scheme 15.

Our initial studies of oxime cycloaddition[51] showed that although the 2:1 adducts were formed in good yield they gave rise to mixtures of all the possible regio- and stereo-isomeric oxazolidines. However, we were attracted by the

[52] R. Grigg and S. Thianpatanagul. *J. Chem. Soc., Perkin Trans. 1*. 1984. 653.

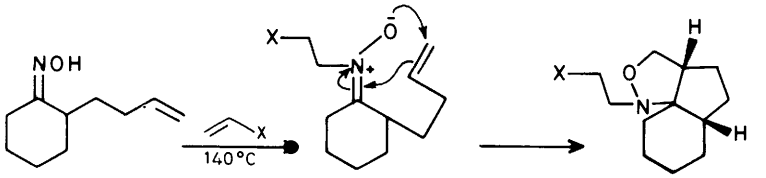
Figure 6 *Potential synthetic variants in oxime cycloadditions*

Michael Addition	*Cycloaddition*
intermolecular	intermolecular
intermolecular	intramolecular
intramolecular	intermolecular
intramolecular	intramolecular



(33) (34)

X = CO_2CH_2Ph or SO_2Ph



100%

X = CO_2CH_2Ph or SO_2Ph

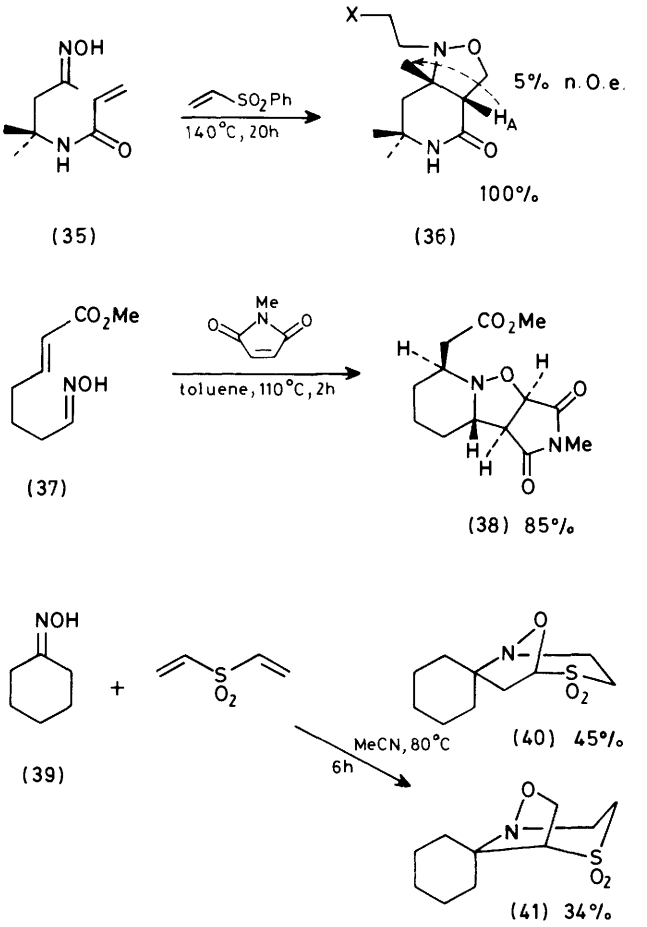
Scheme 16

simplicity of the process and its potential synthetic flexibility. Thus the process consists of two distinct steps (Scheme 14), (i) Michael addition, (ii) cycloaddition, and this provides four broad classes of synthetic methodology (Figure 6).

Further study of oxime cycloadditions was therefore initiated and the process has now been developed into a powerful synthetic method[53] for the construction of complex molecular frameworks. To date examples of the first three classes in Figure 6 have been realised and suitable substrates for the final class are under preparation. The first class, exemplified by (33) ⟶ (34), occurs regiospecifically in excellent yield.

Two typical examples of a large number we have carried out of the second class are shown in Scheme 16 and (35) ⟶ (36). Stereochemistry of the cycloadducts was established by n.O.e. difference spectroscopy. The stereochemistry of the oxime starting material (*syn*, *anti*) is not normally important since under the reaction

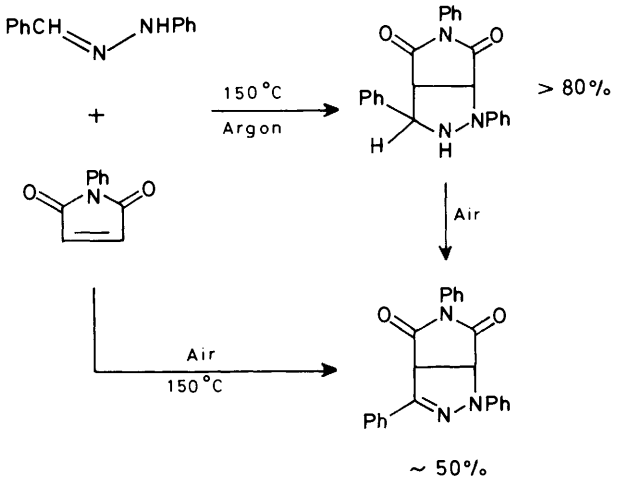
[53] P. Armstrong, R. Grigg, and W. J. Warnock, unpublished observations.



conditions *syn–anti* interconversion is faster than cycloaddition. Thus (35) is a 65:35 mixture of oxime isomers but gives a single cycloadduct (36). A typical example of the third class is shown in (37) ⟶ (38) and the inherent flexibility of this new methodology is further illustrated by processes such as (39) ⟶ (40) + (41) in which oximes react with substrates in which Michael acceptor and dipolarophile are combined within one molecule.

The synthetic manipulation of oxazolidines by reductive cleavage of the N–O bond and their usefulness as precursors of natural products is well known[54] and suggests our new methodology will find many applications in this area.

[54] A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; J. J. Tufariello in '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, Vol. 2. Wiley-Interscience, 1984, p. 83; A. Padwa, *ibid.*, p. 277.



Scheme 17

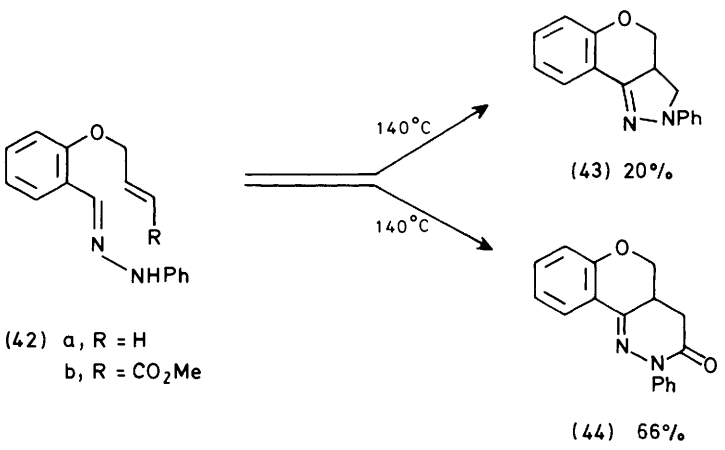
Hydrazones.—These, like oximes, are type III X=Y–ZH systems (Scheme 2) and show a tendency to undergo competing or exclusive Michael additions through carbon as well as 1,3-dipolar cycloadditions *via* a formal 1,2-H shift. Typical 1,3-dipole behaviour is illustrated by the reactions in Scheme 17,[55] which emphasizes the sensitivity of pyrazolidine products to oxidation under the reaction conditions.

Intramolecular reactions to non-activated terminal alkenes, [*e.g.* (42a) ⟶ (43), with accompanying oxidation] or alkynes can also be achieved but in low yield ($\leqslant 20\%$). With activated terminal alkenes (42b) the reaction is diverted to a Michael addition–cyclization process (42b) ⟶ (44).

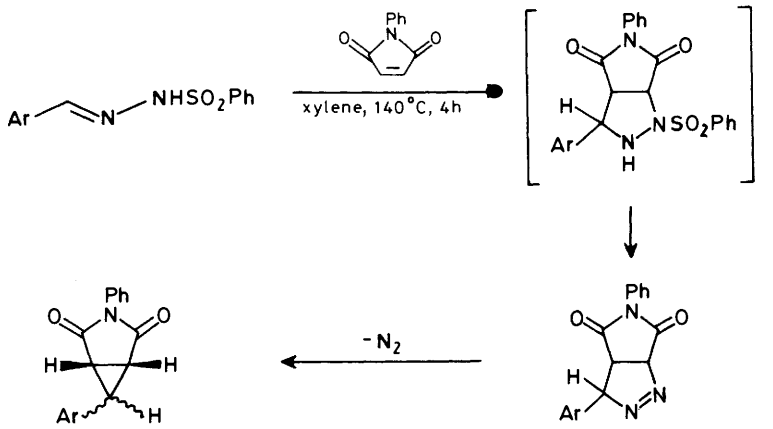
Certain *N*-sulphonylhydrazones on heating with *N*-phenylmaleimide give cyclopropyl derivatives (Scheme 18) *e.g.* Ar = 2-methoxyphenyl, in *ca.* 40% yield[56] and this process can be accommodated by a 1,3-dipolar cycloaddition followed by elimination of sulphinic acid and nitrogen (Scheme 18). Related reactions to Scheme 18 have been reported by others.[57]

Early work of Hesse[58] involving cycloaddition of hydrazones in acid solution has recently been repeated[59] and the 4π-species participating in the cycloaddition is believed to be (45). Type III X=Y–ZH systems have the potential to function as 4π-participants in cycloadditions *via* the neutral (46), *N*-protonated (47) or 1,3-dipolar (6) forms.

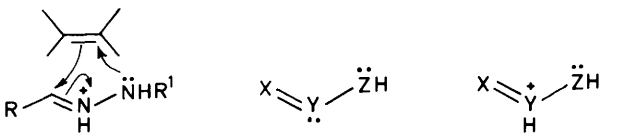
[55] R. Grigg, J. Kemp. and N. Thompson, *Tetrahedron Lett.*, 1978, 2827.
[56] R. Grigg, M. Dowling, and V. Sridharan, unpublished observations
[57] R. M. Wilson, J. W. Rekers, A. P. Packard, and R. C. Elder, *J. Am. Chem. Soc.*, 1980, **102**, 1633; A. G. Schultz, J. P. Dittami, and K. K. Eng, *Tetrahedron Lett.*, 1984, **25**, 1255.
[58] K. D. Hesse, *Annalen*, 1970, **743**, 50.
[59] G. Le Fevre, S. Sinbandhit, and J. Hamelin, *Tetrahedron*, 1979, **35**, 1821.



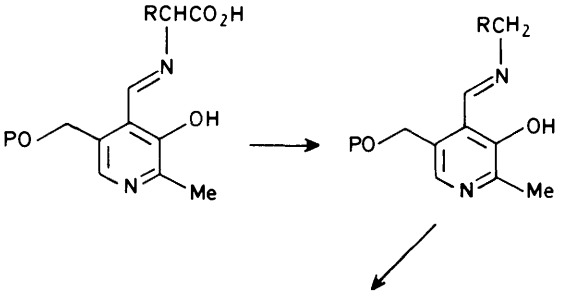
(42) a, R = H
b, R = CO_2Me



Scheme 18



(45) (46) (47)



Scheme 19

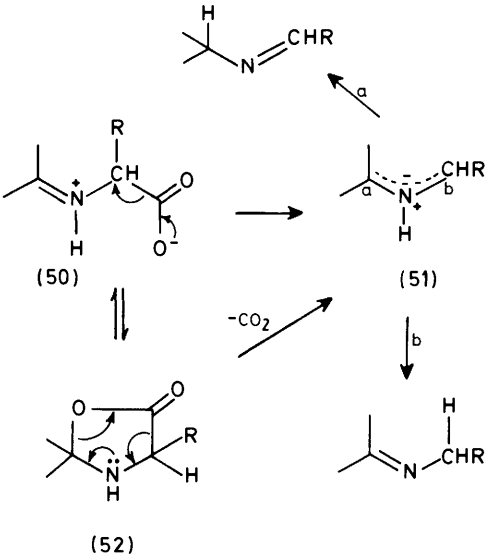
(48) a, X = N
b, X = CH

(49)

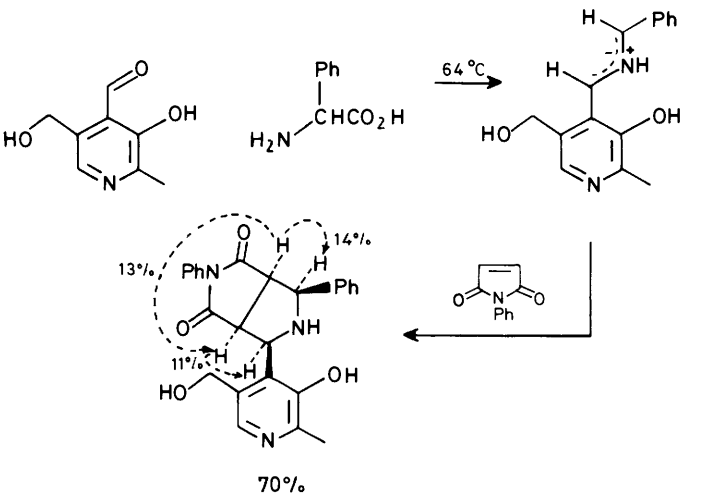
3 Decarboxylative Route to Azomethine Ylides

In the earlier discussion of the biochemistry of pyridoxal imines it was mentioned that decarboxylation of α-amino acids (15) ⟶ (17) is effected *via* imine formation.[60] This is an important biological process leading to the formation of the so-called biogenic amines (Scheme 19) and, as such, has attracted numerous model studies to establish laboratory analogies for the process.[61] Strecker was the first[62] to observe the decarboxylation of an α-amino acid *via* imine formation (with alloxan) in 1862 and the 'carbonyl assisted' *in vitro* decarboxylation of α-amino acids is now known as the Strecker Degradation. Important contributions to the

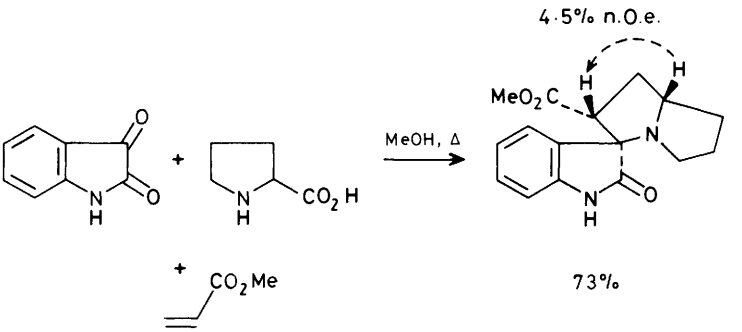
[60] M. H. O'Leary, H. Yamada, and C. J. Yapp, *Biochemistry*, 1981, **20**, 1476; M. H. O'Leary and G. J. Piazza, *ibid.*, p. 2743.
[61] R. M. Herbst, in 'Advances in Enzymology', Vol. 4, Interscience, 1946, p. 75; E. K. Hervill and R. M. Herbst, *J. Org. Chem.*, 1944, **9**, 21.
[62] A. Strecker, *Annalen*, 1862, **123**, 363.



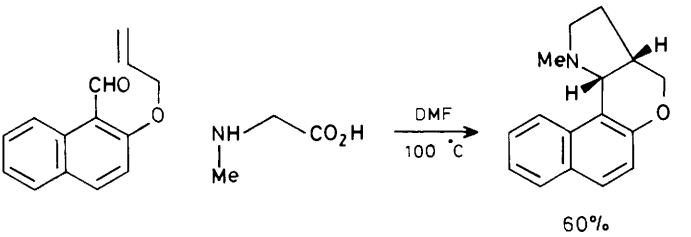
Scheme 20



Scheme 21



Scheme 22



Scheme 23

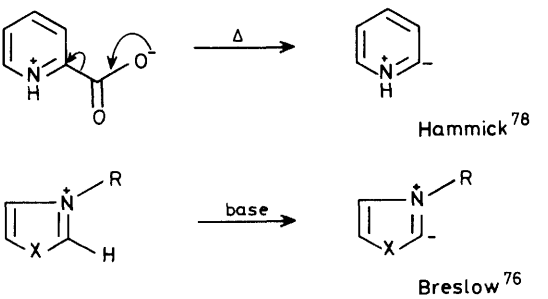
scope and mechanism of the Strecker Degradation have been made by Moubacher and Schonberg,[63] Baddar,[64] and Chatelus.[65]

When we began our work very little synthetic use had been made of the Strecker Degradation and the accepted mechanism (48a) ⟶ (49a) was analogous to that established for β,γ-unsaturated acids (48b) ⟶ (49b).[66] This mechanism seemed unlikely to us. It appeared more probable that the imine would undergo decarboxylation *via* the zwitterionic form (50) (Scheme 20) generating a 1,3-dipole. The final location of the proton in the neutral imine product would then depend on a kinetically controlled proton transfer to the site in the dipole [(51) a or b] with the greatest electron density. The published literature on the Strecker Degradation is readily interpretable in terms of this mechanism, including heretofore unexplained variations in the final site of the imine double bond. Furthermore, the new mechanism is immediately open to a rigorous test by cycloaddition experiments designed to trap the postulated azomethine ylide (51). Such trapping experiments were immediately, and gratifyingly, successful[67,68] and the new method has proved to have a wide synthetic scope. Some typical examples are shown in Schemes 21—23.[67,68]

[63] A. Schonberg and R. Moubacher, *Chem. Rev.*, 1952, **50**, 261.
[64] F. G. Baddar and S. A. M. Sherif, *J. Chem. Soc.*, 1956, 4292 and earlier papers.
[65] J. Chatelus, *Bull. Soc. Chim. France*, 1964, 2523 and earlier papers.
[66] C. A. Buehler and D. E. Pearson, 'Survey of Organic Syntheses', Vol. 2, Wiley, 1977, p. 405.
[67] R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 180.
[68] R. Grigg, M. F. Aly, V. Sridharan, and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 182.

Subsequently we became aware that Rizzi had previously suggested a 1,3-dipolar intermediate for the aldehyde induced decarboxylation of *N*-alkylamino acids under forcing conditions.[69] Fortunately for us he had not appreciated the scope of the process, which will tolerate wide variations in the carbonyl and dipolarophile components and occurs with all types of α-amino acid (primary, secondary; α,α-disubstituted, cyclic, and acyclic). It is not necessary, or usually desirable, to form the imine in a separate step. Merely reacting the amine and carbonyl compound in the presence of a dipolarophile is sufficient. Reaction temperatures range from room temperature to 120 °C. Pyridoxal reacts in hot methanol or in aqueous acetonitrile with phenylglycine and *N*-phenylmaleimide (Scheme 21) to give a single cycloadduct. Adduct stereochemistry in Schemes 21—23 is assigned on the basis of n.O.e. difference spectroscopy and signal enhancement values are indicated in Schemes 21 and 22.

Our initial studies[67,68] led us to comment that dipole production *via* (50) ⟶ (51) (Scheme 20) might be expected to occur with little stereoselectivity compared to dipole formation by the formal 1,2-H shift route (Scheme 3) in which H-bonding is considered to play an important role. However subsequent more detailed studies indicated stereospecific or highly stereoselective dipole formation by the decarboxylative route[70] and requires a revision of our initial suggestion of direct decarboxylation of the zwitterion (50) ⟶ (51). We now believe this process



Scheme 24

Ylide (53) ⟷ Nucleophilic Carbene (54)

[69] G. P. Rizzi, *J. Org. Chem.*, 1970, **35**, 2069.
[70] R. Grigg, S. Surendrakumar, S. Thianpatanagul, and D. Vipond, *J. Chem. Soc., Chem. Commun.*, 1987, 47.

involves an initial stereospecific or highly stereoselective cyclization (50) $\rightleftharpoons$ (52) to an oxazolidin-5-one (Scheme 20) followed by a 1,3-cycloreversion [(52) arrows].[71] 1,3-Cycloreversions are known to occur stereospecifically[72] and Huisgen's extensive work on cycloadditions of mesoionic oxazolones (munchnones)[73] provides numerous examples where transient bicyclic oxazolidin-5-ones gives rise to azomethine ylides by loss of carbon dioxide. Eschenmoser[74] and Seebach[75] have isolated oxazolidin-5-ones and the former author has demonstrated thermal loss of carbon dioxide with formation of a 1,3-dipole. Our work suggests that the possible involvement of oxazolidin-5-ones in the biochemical decarboxylation of α-amino acids by pyridoxal enzymes merits serious consideration.

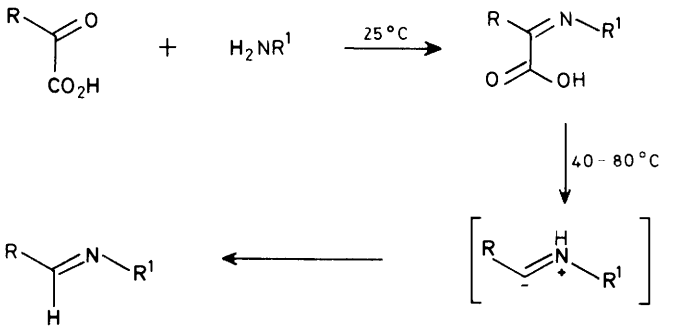
The ninhydrin test referred to earlier in this article involves Strecker Degradation of α-amino acids *via* azomethine ylides as shown by appropriate trapping experiments.[27]

4 Decarboxylative Route to 1,2-Ylides

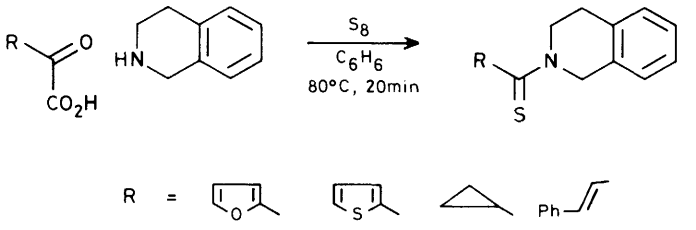
Non-oxidative enzyme-catalysed decarboxylation of α-keto acids to aldehydes involves adduct formation with thiamine pyrophosphate. It is generally considered that this step is essential because α-keto acids lack a suitable 'electron sink' mechanism to stabilize negative charge development during decarboxylation.[76,77] However, it is well known that pyridine-2-carboxylic acid undergoes thermal decarboxylation *via* the zwitterion to give a 1,2-ylide (Scheme 24) which can be trapped by electrophiles (Hammick reaction).[78] Furthermore, the ready deprotonation of azolium cations at C(2) (Scheme 24) to give a 1,2-ylide is the basis of the biochemistry of thiamine pyrophosphate[76] and important synthetic methodology for C–C bond formation.[79]

Thus the moiety (53) possesses intrinsic stabilizing features when part of an aromatic ring system in which R is a heteroatom or an sp^2-carbon centre. This enhanced stability is usually attributed to carbene resonance (53) $\longleftrightarrow$ (54), but it is unclear what, if any, contribution the presence of the aromatic ring makes to this enhanced stability. Acyclic examples of (53) might be generated by decarboxylation of imines of α-keto acids and this encouraged us to study such processes. The imines (Scheme 25) are readily prepared at ambient temperature and smoothly

[71] R. Grigg, J. Idle, P. McMeekin, and D. Vipond, *J. Chem. Soc., Chem. Commun.*, 1987, 49.
[72] G. Bianchi and R. Gandolfi, in '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, Vol. 2, Wiley-Interscience, 1984, p. 451.
[73] R. Huisgen, 'Aromaticity', Chemical Society Special Publication No. 21, 1967, p. 51; R. Huisgen, H. Gotthardt, and H. O. Baeyer, *Chem. Ber.*, 1970, **103**, 2368; *J. Am. Chem. Soc.*, 1970, **92**, 4340.
[74] A. Eschenmoser, *Chem. Soc. Rev.*, 1976, **5**, 377.
[75] D. Seebach, M. Boes, R. Naef, and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
[76] R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719; J. Duclos and P. Heake, *Biochemistry*, 1974, **13**, 5358; M. Begtrup, *J. Chem. Soc., Chem. Commun.*, 1975, 344.
[77] J. Crosby, R. Sine, and G. Lienhard, *J. Am. Chem. Soc.*, 1970, **92**, 2891; T. Lowe and L. Ingram, 'An Introduction to Biochemical Reaction Mechanisms', Prentice-Hall, New Jersey, 1975, pp. 71 *et seq.*
[78] P. Dyson and D. Ll. Hammick, *J. Chem. Soc.*, 1937, 1724; M. R. F. Ashworth, R. P. Daffern, and D. Ll. Hammick, *ibid.*, 1939, 809.
[79] H. Stetter and G. Dambkes, *Synthesis*, 1977, 403; H. Stetter, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 639.



Scheme 25



Scheme 26

decarboxylate in boiling methylene chloride or benzene to give the corresponding decarboxylated imines (Scheme 25, R = R^1 = alkyl or aryl).

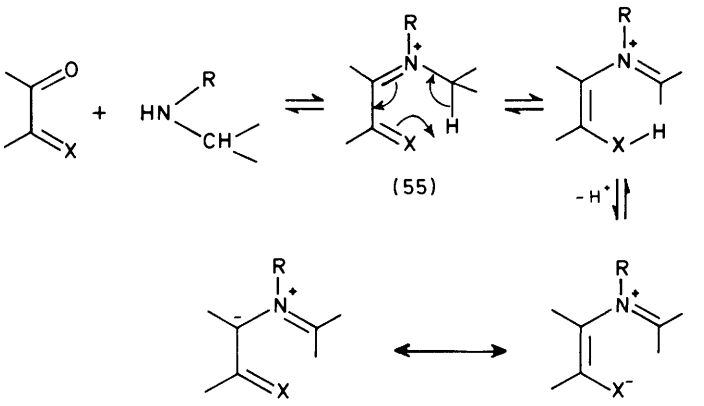
Attempts to trap the intermediate, 1,2-ylide with aromatic aldehydes were unsuccessful. Transimination and competitive proton transfer, to give the decarboxylated imine, intervene. However, the 1,2-ylide can be trapped with sulphur to give the corresponding thioamide in excellent yield and this can be achieved in a one-pot reaction from primary or secondary amines, α-keto acid and sulphur, *e.g.* Scheme 26.[80] Further reactions of (53) ⟷ (54) are under study.

Thus the decarboxylation of α-keto acids *via* imine formation is a facile process and it would be surprising if there are no biochemical processes utilizing this reaction.

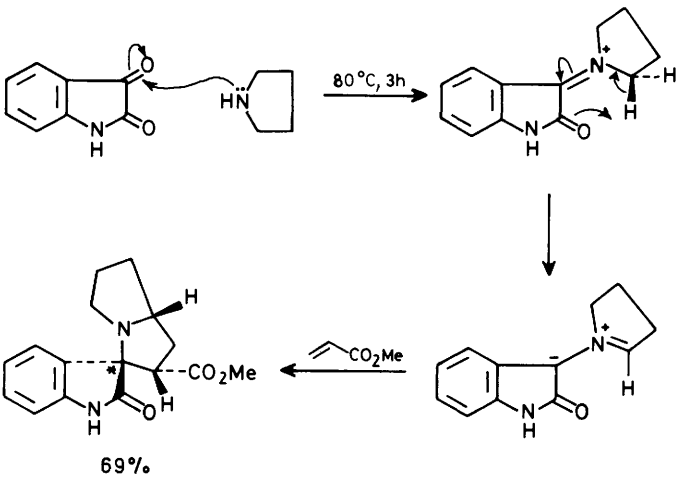
5 The Iminium Ion Route to Azomethine Ylides

The concept of a 1,5-H shift facilitating dipole formation that proved successful in the oxime case (Scheme 15)[52] might, we felt, be applied to the generation of azomethine ylides from unactivated primary and secondary amines as outlined in Scheme 27.

[80] M. F. Aly and R. Grigg, *J. Chem. Soc., Chem. Commun.*, 1985, 1523.



Scheme 27

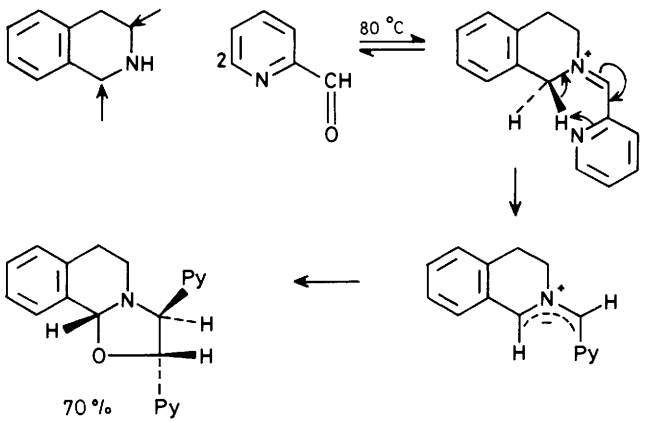


Scheme 28

Sigmatropic rearrangements in charged systems are generally extraordinarily facile[81] but to our knowledge this concept of charge acceleration has not been applied to 1,5-shifts[82] such as [(55) arrows] (Scheme 27). It proved remarkably simple to generate azomethine ylides from primary and secondary amines and

[81] H. J. Hansen, B. Sutter, and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 828; D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765; M. Koreeda and J. I. Luengo, *ibid.*, 1985, **107**, 5572.

[82] For a related 1,6-H shift leading to 1,5-dipoles see A. N. Reinhoudt, G. W. Visser, W. Verboom, P. H. Benders, and M. L. M. Pennings, *J. Am. Chem. Soc.*, 1985, **105**, 4775.



Scheme 29

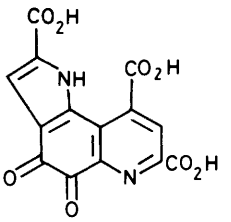
carbonyl compounds containing the moiety O=C–C=X.[83] A survey of carbonyl compounds of this latter type has shown that ninhydrin, isatin, acenaphthaquinone, phenylglyoxaldehyde, ethyl glyoxylate, and pyridine-2-carbaldehyde all function as suitable precursors of azomethine ylides. Examples where X=S (Scheme 27) have yet to be studied. Typical examples of this new route to azomethine ylides are shown in Schemes 28 and 29.[83] In each case a single stereoisomer is obtained and in Scheme 29 the reaction is regiospecific, involving only the benzylic methylene group.

The stereochemistry of the cycloadducts in Schemes 28 and 29 are assigned by n.O.e. difference spectroscopy except for that at C* in Scheme 28 which is tentative and is assigned in accord with the proposed mechanism. It must be admitted that although these reactions provide a facile route to azomethine ylides, alternative, non-sigmatropic, base-catalysed mechanisms may be operative. Thus 3,5-di-tert-butyl *o*-benzoquinone[84] and phenylglyoxaldehyde[85] react with amines to give ketones *via* prototropy of the intermediate imines and the mammalian and bacterial coenzyme methoxatin (56) functions similarly.[86] Thus a non-sigmatropic, base-catalysed process has much to commend it. Dipole stereochemistry in this case would then be controlled by the stabilization afforded by a 1,5-charge interaction (57).[83]

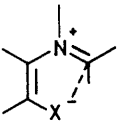
6 Metallo-1,3-Dipoles

In the general dipole equilibrium (5) $\rightleftharpoons$ (6) any atom, X, Y, Z, or H could conceptually be replaced by a metal ion and this raises many intriguing possibilities.

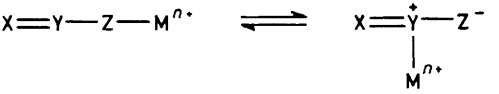
[83] H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatanagul, and S. Kanajun, *J. Chem. Soc., Chem. Commun.*, 1986, 602.
[84] E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, 1969, **91**, 1429.
[85] V. Calo, L. Lopez, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1652.
[86] C. L. Lobenstein-Verbeck, J. A. Jongejan, J. Frank, and J. A. Duine, *FEBS Lett.*, 1984, **170**, 305; Y. Ohshiro, S. Itoh, K. Kurokawa, J. Kato, T. Hirao, and T. Agawa, *Tetrahedron Lett.*, 1983, **24**, 3465; S. Itoh, M. Mure, Y. Ohshiro, and T. Agawa, *ibid.*, 1985, **26**, 4225.



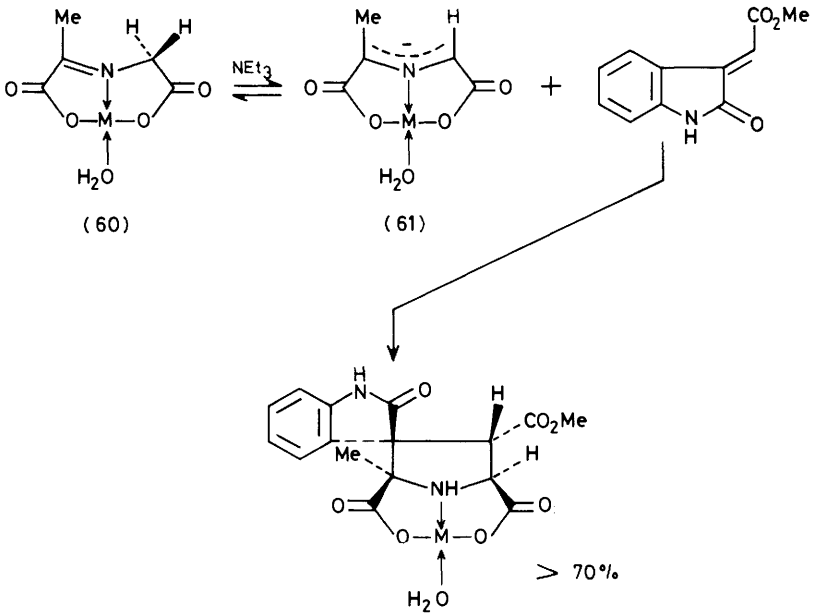
(56)



(57)

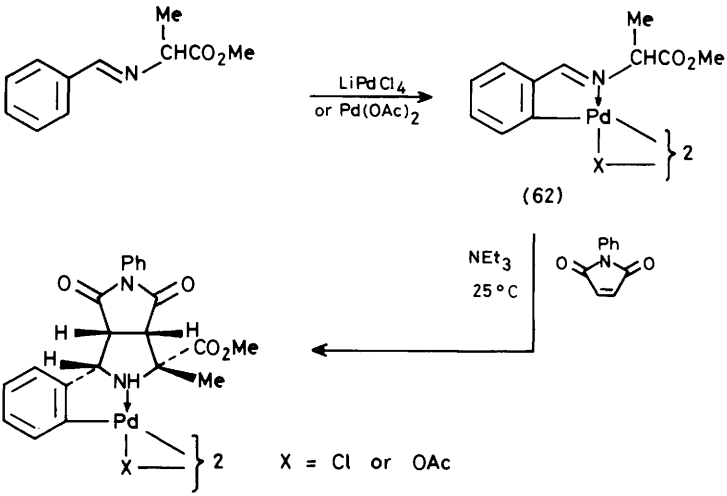


(58) (59)



(60) (61)

Scheme 30



Scheme 31

We have initially focussed on examples in which H is replaced by a metal ion (58) $\rightleftharpoons$ (59) and, although we have, as yet, no metallotropic examples we have several examples of (59).[29,37] A family of metallo-1,3-dipoles (59) can be imagined in which the overall molecular charge will vary with the valency of the metal ion M and the number of associated counterions. In a development of earlier work by Casella *et al.*[87] we prepared a series of copper(II), zinc(II), and cadmium(II) complexes of imines derived from α-keto acids and glycine or alanine. These metal complexes, *e.g.* (60), undergo stereo- and regio-specific cycloadditions to 1,2-disubstituted electronegative olefins in the presence of weak base at ambient temperature *via* the metallo-1,3-dipole (61) (Scheme 30).[88] Reactions of these metallo imines with methyl acrylate, phenyl vinyl sulphone, and acrylonitrile frequently give mixtures of regio- and stereo-isomers. The stereoisomers arise by isomerization of initial cycloadducts formed by a $4\pi + 2\pi$ concerted process.

The reaction of aryl imines of α-amino acid esters with either lithium tetrachloropalladate or palladium acetate gives the corresponding dimeric ortho palladated imines (62) (Scheme 31) in good yield. These imines (62) are readily deprotonated by weak base at ambient temperature and the resulting metallo-1,3-dipole can be trapped by *N*-methylmaleimide in good yield (Scheme 31).[89]

The work described in this article has all developed from the simple idea of 1,2-protopropy in X=Y–ZH systems and the extension of this and related ideas is still developing rapidly.

[87] L. Casella, M. Gullotti, and E. Melani, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1827.
[88] R. Grigg, V. Sridharan, and S. Thianpatanagul, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1669.
[89] R. Grigg and J. Devlin, *J. Chem. Soc., Chem. Commun.*, 1986, 631.

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