Iminium Ion Route to Azomethine Ylides from Primary and Secondary Amines

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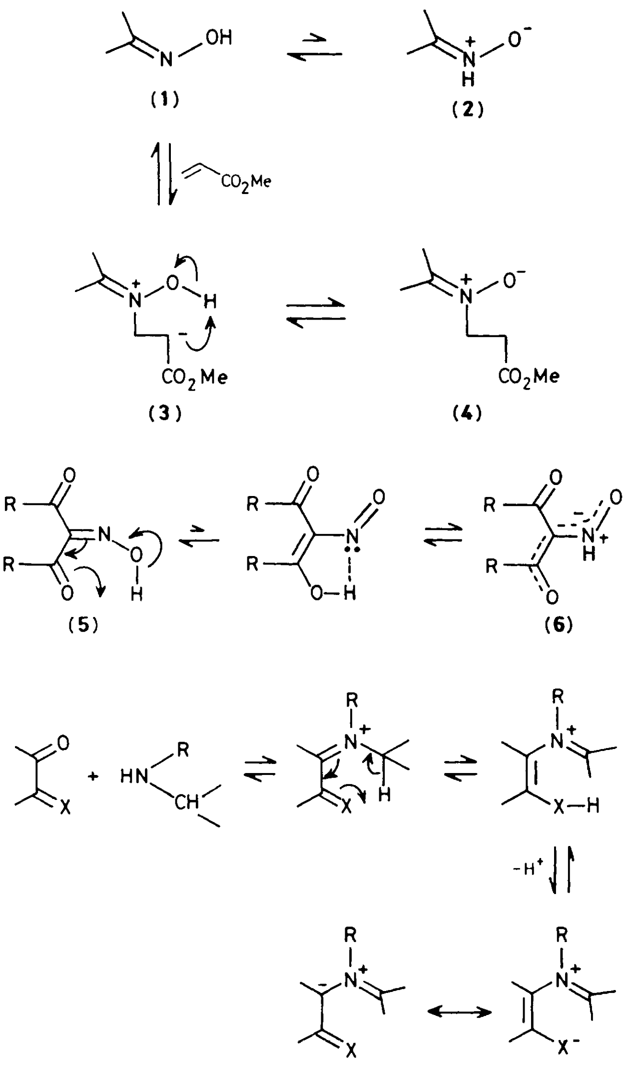
Iminium ion formation between primary or secondary amines and carbonyl compounds containing the moiety O=C–C=X results in a facile and stereospecific generation of azomethine ylides which can be trapped in 1,3-dipolar cycloaddition reactions.

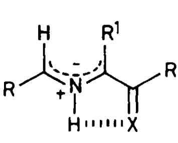
We have recently developed two new prototropic routes to 1,3-dipoles involving either a formal 1,2-H shift in X=Y–ZH systems[1] or decarboxylation of imines of α-amino acids.[2] The formal 1,2-H shift in oximes, (**1**) $\rightleftharpoons$ (**2**), was found to be disfavoured energetically with respect to dipole generation *via* a Michael addition of the nitrogen lone pair to the dipolarophile followed by a proton transfer, *e.g.* (**1**) → (**3**) → (**4**).[3] Subsequently we were able to generate (**2**) in special cases, *e.g.* (**5**) → (**6**), where a 1,5-H shift facilitated 1,3-dipole formation.[4]

This concept of a 1,5-H shift facilitating dipole formation might be applied to the generation of azomethine ylides from

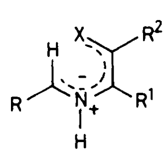


Scheme 1

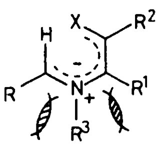
unactivated primary and secondary amines as outlined in Scheme 1. This route to 1,3-dipoles[†] would accord with the extensive work on the Strecker degradation by Schonberg, Moubasher, and their co-workers.[5] Sigmatropic rearrangements in charged systems are generally faster than in the corresponding neutral systems and important examples of the effect of charge in i,j-shifts have been reported[6] but to our knowledge the concept of acceleration has not been employed for 1,5-shifts.[7] The mechanism proposed in Scheme 1 provides an inbuilt preference for one dipole configuration when primary amines of the type RCH_2NH_2 are used.[‡] Our previously reported prototropic dipole generation results in stereospecific formation of (**7**),[1] whilst the sigmatropic route would generate (**8**) stereospecifically. When secondary amines are used buttressing effects (**9**) should influence the kinetically preferred dipole.



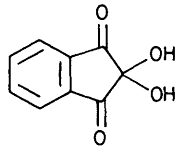
(**7**)



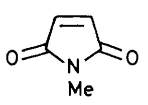
(**8**)



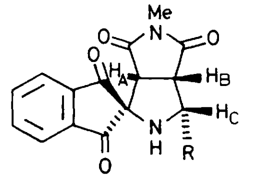
(**9**)



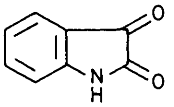
(**10**)



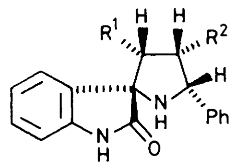
(**11**)



(**12**) R = p-$MeOC_6H_4$



(**13**)



(**14**) **a**; $R^1 = CO_2Me$, $R^2 = H$
b; $R^1 = H$, $R^2 = CO_2Me$

A survey of carbonyl compounds containing the moiety O=C–C=X (Scheme 1) has shown that ninhydrin, isatin, acenaphthaquinone, phenylglyoxaldehyde, ethyl glyoxylate, and pyridine-2-carbaldehyde all function as suitable precursors of dipoles. Examples where X = S (Scheme 1) have yet to be studied.

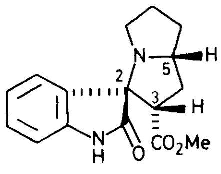
Ninhydrin (**10**) reacts (MeCN, 80 °C, 24 h) with *p*-methoxybenzylamine and *N*-methylmaleimide (**11**) to give a 7.7:1 mixture (73%) of *endo*- and *exo*-cycloadducts in which (**12**) is the major isomer. The stereochemistry of all the cycloadducts described in this paper is assigned on the basis of nuclear Overhauser effect difference spectroscopy (n.O.e.d.s.); *e.g.* irradiation ($CDCl_3$) of the signal for H_B in (**12**) results in enhancements of the signals for H_C (13.5%) and H_A (26%). Isatin (**13**), benzylamine, and methyl acrylate react (MeCN, 80 °C, 6 h) to give a 5:2 mixture (60%) of regioisomers (**14a** and **b**).

Secondary amines react in an analogous fashion to primary amines. Thus pyrrolidine, isatin (**13**), and methyl acrylate (MeCN, 80 °C, 3 h) react to give (**15**) (69%). The stereochemistry of (**15**) at C(2) is assigned from mechanistic considerations whilst that at C(3) and C(5) rests on an n.O.e.d.s. enhancement ($CDCl_3$) of the signal for the C(3)-H of 4.5%, on irradiation of the C(5)-H.

1,2,3,4-Tetrahydroisoquinoline and tetrahydro-β-carboline undergo regiospecific dipole formation at the benzylic position. Thus both amines react with two moles of pyridine-2-carbaldehyde (MeCN, 80 °C) to give (**16**) (70%) and (**17**) (64%) respectively.

[†] Strictly speaking the dipoles in Scheme 1 are 1,5-dipoles but the particular examples discussed herein function as 1,3-dipoles in their cycloaddition reactions.

[‡] Only one imine configuration has the correct geometry for the 1,5-H shift. However, only a small equilibrium concentration of the required isomer is necessary for the process to proceed.



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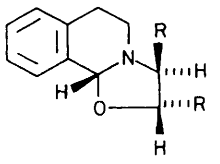
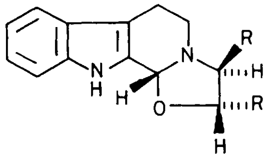


(16) R = 2-pyridyl



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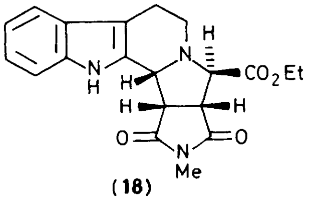

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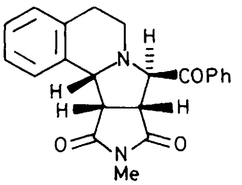

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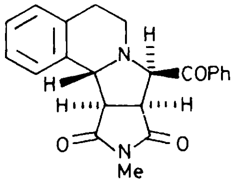

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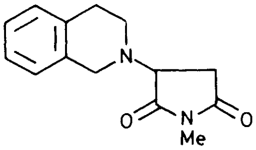

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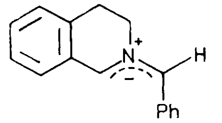

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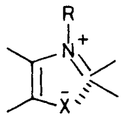

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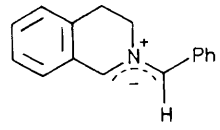

(23)

Tetrahydro-β-carboline reacts (MeCN, 80 °C, 15 h) with ethyl glyoxylate and (**11**) to give a single cycloadduct (**18**) (60%) whilst tetrahydroisoquinoline, phenyl glyoxaldehyde, and (**11**) give (MeCN, 80 °C, 2 h) a 7 : 1 mixture of *endo*-(**19**)- and *exo*-(**20**)-cycloadducts (75%) together with *ca.* 20% of the Michael adduct (**21**).

Although the stereochemistry of cycloadducts reported herein accords with the 1,5-shift mechanism outlined in Scheme 1, alternative mechanistic interpretations are possible. Thus non-stereospecific dipole formation occurs when benzaldehyde and 1,2,3,4-tetrahydroisoquinoline are heated (toluene, 110 °C) in the presence of (**11**), showing that dipole formation by deprotonation of intermediate iminium species is occurring. The cycloadducts (mixtures of *endo*- and *exo*-isomers) reflect a *ca.* 7:2 ratio of *anti*-(**22**) and *syn*-(**23**) dipoles. Huisgen has briefly reported the deprotonation of two 3,4-dihydroisoquinolinium salts to give dipoles of unknown stereochemistry[8] and a simple deprotonation mechanism could also account for the results with carbonyl compounds containing the O=C–C=X moiety with steric and/or electronic factors favouring one dipole configuration *e.g.* terminal charge interaction in the 1,5-dipole (**24**).

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References

1 R. Grigg, *Bull. Soc. Chim. Belg.*, 1984, **93**, 593; R. Grigg, H. Q. N. Gunaratne, and J. Kemp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 41.
2 R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 180; R. Grigg, M. F. Aly, V. Sridharan, and S. Thianpatanagul, *ibid.*, 1984, 182.
3 R. Grigg, M. Jordan, A. Tangthongkum, F. W. B. Einstein, and T. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1984, 47.
4 R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Perkin Trans. 1*, 1984, 653.
5 A. Schonberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 1948, 176; A. Schonberg and R. Moubasher, *ibid.*, 1950, 1422.
6 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.
7 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.
8 R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1963, 1441.