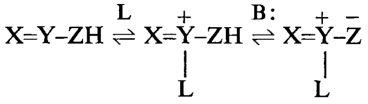
Brönsted and Lewis Acid Catalysis of X=Y–ZH Cycloadditions

R. Grigg* and H. Q. N. Gunaratne

Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland, U.K.

Cycloadditions of arylidene imines of methyl phenylglycinate show substantial rate enhancements in the presence of Brönsted and Lewis acids; for Brönsted acids the rate is related to the pK_a of the acid, whilst for the Lewis acids studied the rate acceleration decreased in the order $Zn(OAc)_2 > AgOAc > LiOAc > Mg(OAc)_2$.

Catalysis of 6π-electron cycloadditions by complex formation between a Lewis acid and the dienophile (Diels–Alder)[1] or enophile (ene reaction)[2] is well known. Following our studies of both inter[3]- and intra[4]-molecular cycloadditions of X=Y–ZH systems, we report here a series of acid-catalysed cycloadditions in which Brönsted and Lewis acids



$$X{=}Y{-}ZH \rightleftharpoons X{=}\overset{+}{\underset{L}{\overset{L}{Y}}}{-}ZH \rightleftharpoons X{=}\underset{L}{\overset{+}{Y}}{-}\overset{B:\ \ -}{Z}$$

Scheme 1. L = H^+ or Lewis acid.

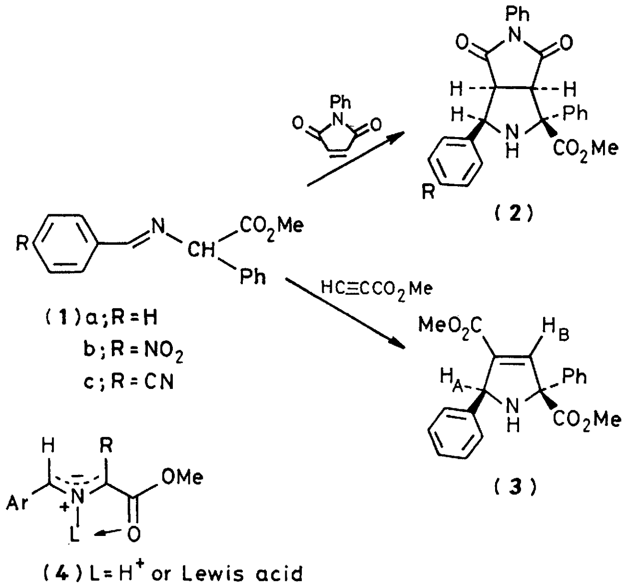


Table 1.[a] Effect of pK_a of acid catalyst on the half life for the cycloaddition of the Schiff's base (**1**) and *N*-phenylmaleimide in [$^2H_8$]toluene.

Schiff's base	Acid	pK_a of acid	$t_{\frac{1}{2}}$/min[c]	Temp./ °C[b]
(**1a**)	—		120 ± 4	105
(**1a**)	2-Pyridone	11.99	88 ± 6	105
(**1a**)	$MeCO_2H$	4.75	6[d]	105
(**1a**)	Meldrum's acid[e]	5.1	5[d]	105
(**1a**)	2,4-Dinitrophenol	4.0	3[d]	105
(**1b**)	—	—	668 ± 8	105
(**1b**)	$MeCO_2H$	4.75	56 ± 4	95
(**1c**)	—	—	583 ± 7	105

[a] Kinetics were measured in the probe of a Bruker WH90 spectrometer, spectral width 1000 Hz, 4K data points. [b] Temperature accurate to ±0.5 °C. [c] Errors refer to statistical errors. [d] Approximate values of $t_{\frac{1}{2}}$. [e] 2,2-Dimethyl-1,3-dioxan-4,6-dione.

promote 1,3-dipole formation from imines (Scheme 1).† These processes differ from the above 6π-cycloadditions, which involve complexation of 2π-components, in that complexation of the 4π-component is involved.

We have studied the effect of Brönsted acids on the cycloaddition (**1**) → (**2**) (Table 1) and Lewis acids on the cycloaddition (**1**) → (**3**); (Table 2). The reactions proceeded cleanly and in high yield with no evidence of decomposition apart from a little hydrolysis of the Schiff's base (**1**). The stereochemistry of (**2**) and (**3**) is assigned on the basis of our earlier studies.[3] The cycloaddition (**1**) → (**3**) is regiospecific and the regiochemistry is assigned on the basis of the n.m.r. spectrum of (**3**) which shows only a small coupling constant between H_A and H_B (*J* 1.95 Hz).‡

Table 2.[a] Effect of Lewis acids on the half life for the cycloaddition of the Schiff's base (**1a**) and methyl propiolate in [$^2H_8$]toluene (80 °C).

Lewis acid[b]	$t_{\frac{1}{2}}$/h	Yield (%)[c]
—	38	94
$MeCO_2H$	1.8	—
$Zn(OAc)_2.2H_2O$	3.0	88
AgOAc	3.25	95
$LiOAc.2H_2O$	5.5	93
$Mg(OAc)_2$	8.75	—

[a] Reactions were run in a thermostatted oil bath; temperature variation ±0.5 °C. [b] The metal salts only partially dissolved in the hot solvent. [c] Estimated by n.m.r. spectroscopy using hexamethylbenzene as internal standard.

The half life ($t_{\frac{1}{2}}$) for the cycloaddition (**1**) → (**2**) was found to be dependent on the pK_a of added protonic acids (Table 1).§ Reactions were performed in sealed n.m.r. tubes with equimolar amounts of the Schiff's base (**1**) and the acid dissolved in [$^2H_8$]toluene (0.4 M). The fastest rate was observed with 2,4-dinitrophenol, the strongest acid of those studied, whilst the slowest rate was observed with 2-pyridone, the weakest acid studied.¶

Enhanced rates of the cycloaddition (**1**) → (**2**) in the absence of added acid were also observed when [$^2H_8$]-toluene was replaced by CD_3NO_2 (pK_a 10.6) as solvent.** Thus, the $t_{\frac{1}{2}}$ values for (**1a**) (59.8 min), (**1b**) (160 min), and (**1c**) (175 min) were substantially less in CD_3NO_2 than in [$^2H_8$]toluene (Table 1).

Analogous rate enhancements were observed using metal salts as Lewis acid catalysts for the process (**1a**) → (**3**) (Table 2).§ Use of $AlCl_3$ as Lewis acid catalyst tends to divert the reaction to pyrrole formation.[5]

The activity of lithium acetate (Table 2) is of particular interest in the light of Kauffmann's extensive studies on anionic cycloadditions of lithium salts of 2-aza-allyl anions.[6] These lithium aza-allyl species may thus be a further example of the general dipolar species depicted in Scheme 1 in which L = Li^+. In our examples dual co-ordination to the imine nitrogen and ester oxygen atoms [structure (**4**)] is thought to be important.

---

† Other species, *e.g.*, $X{=}Y{-}\overset{+}{Z}(H){-}L$, are also expected to be present and in certain cases may, depending on the nature of X, Y, and Z, retard the reaction.

‡ Coupling constants for C*H*–C*H*= are 6.5—11.5 Hz. Four-bond 'W' coupling constants for C*H*–C=C*H* are 1.5—2.5 Hz and are dependent on the angle between the protons: A. J. Gordon and R. A. Ford, 'The Chemists Companion,' Wiley-Interscience, New York, 1972, p. 273.

§ Progress of the reaction was followed by plotting R/(R + P) against time where R = reactant Schiff's base and P = cycloadduct.

¶ *Added in proof:* We have recently found that the cycloaddition (**1**) → (**2**) can be carried out at room temperature in acetic anhydride containing a little acetic acid [*e.g.* (**1**; R = OMe) → (**2**; R = OMe; 79%) in 2 h], or in acetonitrile containing 10% acetic acid.

** This rate enhancement may be partly due to solvent polarity.

We thank the S.R.C. and Queen's University for support.

Received, 30th October 1981; *Com. 1273*

References

1 K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4094; T. Inukai and T. Kojima, *J. Org. Chem.*, 1967, **32**, 869, 872; *Can. J. Chem.*, 1971, **36**, 924; A. W. McCulloch and A. G. McInnes, *ibid.*, 1971, **49**, 3152; J. S. Tou and W. Reusch, *J. Org. Chem.*, 1980, **45**, 5013; P. C. Jain, Y. N. Mukerjee, and N. Anand, *J. Am. Chem. Soc.*, 1974, **96**, 2996.

2 B. B. Snider, *J. Org. Chem.*, 1981, **46**, 3155; M. J. Begley, J. P. Benner, and G. B. Gill, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1112; M. Orfanopoulos and L. M. Stephenson, *J. Org. Chem.*, 1981, **46**, 2201.

3 R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1978, 2823; 1980, 2461; R. Grigg, J. Kemp, G. Sheldrick, and J. Trotter, *J. Chem. Soc., Chem. Commun.*, 1978, 109.

4 R. Grigg, M. Jordan, and J. F. Malone, *Tetrahedron Lett.*, 1979, 3877.

5 R. Grigg, N. Gunaratne, and J. Kemp, unpublished observations.

6 W. Bannworth, R. Eidenschink, and T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 468; T. Kauffmann, H. Ahlers, A. Hamsen, H. Schulz, H.-J. Tilhard, and A. Vahrenhorst, *ibid.*, 1977, **16**, 119.