Steric and Electronic Effects on 2(1*H*)-Pyridone Cycloadditions

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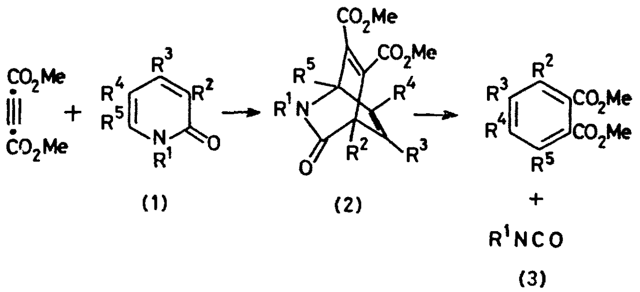
Summary The addition of dimethyl butynedioate to a variety of 2(1*H*)-pyridones is reported and the effect of the different substituents discussed.

PREVIOUS reports on cycloadditions involving 2(1*H*)-pyridones have emphasised the vigorous conditions required for reaction and the low yields of cycloadducts generally observed.[1] Herein are described some recent results in this area which indicate that both steric and electronic effects influence the ease of cycloaddition of dimethyl butynedioate across the 3,6-positions of the 2(1*H*)-pyridone system (**1**).



a; $R^1 = R^5 = Me; R^2 = R^3 = R^4 = H$
b; $R^1 = R^2 = Me; R^3 = R^4 = R^5 = H$
c; $R^1 = R^4 = R^5 = Me; R^2 = R^3 = H$
d; $R^1 = R^3 = R^5 = Me; R^2 = R^4 = H$
e; $R^1 = Me; R^2 = R^3 = R^4 = H; R^5 = OMe$
f; $R^1 = Me; R^2 = R^4 = R^5 = H; R^3 = Ph$
g; $R^1 = R^5 = Me; R^2 = R^4 = H; R^3 = Ph$
h; $R^1 = OMe; R^2 = R^4 = H; R^3 = R^5 = Me$

TABLE[a]

Pyridone	M.p./°C	% Reaction[b]	Product	Isolated yield/%
(**1a**)	56	22	(**2a**)	20
(**1b**)	Liquid	0	—	0
(**1c**)	91—92	75	(**2c**)	70
(**1d**)	86	(31)[c]	(**2d**)	31
(**1e**)	53	0	—	0
(**1f**)	140	0[d]	—	0
(**1g**)	106	73	(**2g**)	70
(**1h**)		0[c,e]	—	0

[a] All new compounds were fully characterised. [b] Reactions were followed by ^{1}H n.m.r. spectroscopy, monitoring the disappearance of the starting *N*-methyl signal against appearance of product(s). Reactions were carried out in 1·6 M pyridone solutions in acetonitrile at 80 °C for 72 h. [c] From the work of Heep (ref. 1e). In this paper the yield of product is incorrectly quoted (see the experimental section). The corrected yield is as stated in the Table. [d] Traces were detected. Reaction in neat dimethyl butynedioate at 80 °C for extended time gave the adduct (**2f**) in 36% yield. [e] Traces were detected. Reaction under the standard conditions for 170 h gave the adduct (**2h**) in 8% yield.

Our results are presented in the Table. Cycloadditions were carried out in acetonitrile at 80 °C in sealed glass tubes at standard concentrations using 1·1 equiv. of the ester. The starting pyridones were synthesised by standard methods.[2] *N*-Methylation was accomplished using the procedure of Hopkins *et al.*[3] Reactions were monitored by disappearance of the *N*-methyl signal of the starting material in the ^{1}H n.m.r. spectrum. Under the standard conditions the product was generally the bicyclic adduct (**2**). More vigorous reaction conditions, *e.g.* 140 °C for 14 h, gave the product arising from the retro-Alder breakdown of the cycloadducts, *i.e.* the phthalic ester (**3**). Although the pyridone (**1f**) did not afford any adduct under the standard reaction conditions, heating it in neat dimethyl butynedioate for long periods at 80 °C did produce the bicycloadduct (**2f**) in moderate yields (36%). A low yield (8%) of the bicyclo-adduct (**2h**) was produced when the pyridone (**1h**) was heated under the standard conditions for 170 h.

Early investigations used *N*-methyl-2(1*H*)-pyridone as a diene (*N*-methylated to avoid the otherwise ready Michael addition with acceptor dienophiles[1d]). Results were generally poor, leading some workers to infer that the classical compatibility of electron-rich diene and electron-deficient dienophile was inapplicable for this pyridone system and that it was behaving as an electron deficient diene (inverse electron demand). The experiments used to examine this possibility were, however, inconclusive.[4] Molecular orbital calculations (CNDO/2[5] and *ab initio*[6]) suggested that pyridone should be a neutral diene[7] and, accordingly, the tabulated experiments were designed to test the effect of substituents.

A comparison of the results for the methyl-substituted pyridones (**1a**—**1d**) shows that substitution into position 6 has the greatest effect on the rate of cycloaddition. That this is primarily a steric rather than an electronic effect is supported by a comparison of the results for the pyridones (**1c**) and (**1d**). In the former case the 6-methyl group is buttressed against both the 1- and 5- methyl groups. When the same substituents are separated, as in (**1d**), the rate of cycloaddition is substantially decreased. A comparison of (**1e**) with (**1a**) shows a consistent trend; if the electronic influence were of primary importance at the 6-position one would expect, classically, the rate of addition to be greater for (**1e**). Since the methyl group is bulkier, with respect to its buttressing effect, than a methoxy group, a steric effect is again implied. The same argument also applies to the conjugated pyridone (**1f**), which gives no adduct under the reaction conditions, although a combination of both steric and electronic effects as in (**1g**) does show a significant improvement.

Similar steric effects have been noted by Bradsher.[8] The suggestion that pyridones are of the inverse demand type is not supported by this work, although the possibility of successful cycloadditions between electron-rich dienophiles and appropriately substituted pyridones, bearing electron-withdrawing groups, cannot be discounted.

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[1] (a) B. S. Thyagarajan and K. Ragagopalan, *Tetrahedron*, 1963, **19**, 1483; (b) B. S. Thyagarajan, K. Ragagopalan, and P. V. Gopalakrishnam, *J. Chem. Soc.* (*B*), 1968, 300; (c) H. Tomisawa and H. Honge, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 925, 941; (d) R. M. Acheson and P. A. Tasker, *J. Chem. Soc.* (*C*), 1967, 1542; (e) U. Heep, *Tetrahedron*, 1975, **31**, 77.

[2] R. A. Abramovitch, 'Heterocyclic Compounds,' Wiley, 1975, Vol. 14.

[3] G. C. Hopkins, J. P. Janak, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, 1967, **32**, 4040.

[4] E. B. Sheinin, G. E. Wright, C. L. Bell, and L. Bauer, *J. Heterocyclic Chem.*, 1968, **5**, 859.

[5] P. A. Dobosh and C. J. Finder, Program 223, Q.C.P.E., Indiana University, 1972.

[6] W. J. Hehre, W. A. Latham, R. Ditchfield, M. D. Newton, and J. A. Pople, Gaussian 70, Program 236, Q.C.P.E., Indiana University, 1971.

[7] R. Sustmann, *Tetrahedron Letters*, 1971, 2721.

[8] C. K. Bradsher, N. A. Porter, and T. G. Wallis, *J. Org. Chem.*, 1974, **39**, 1172.