

Diels–Alder Cycloaddition Reaction of Unactivated 2-Aza-1,3-dienes with Dialkyl Azodicarboxylates and Heterocumulenes

José Barluenga,* Francisco J. González, Santos Fustero, and Vicente Gotor

Departamento de Química Orgánica, Facultad de Química, Universidad de Oviedo, 33071, Spain

The first example is presented of a Diels–Alder cycloaddition of electronically neutral 2-aza-1,3-dienes using an electron-poor dienophile; the [4 + 2] cycloaddition reaction of 2-aza-1,3-dienes to heterocumulenes and carbon disulphide is also shown.

Since its discovery, the Diels–Alder reaction has largely proved to be one of the most valuable, versatile processes for constructing organic molecules.^{1,2} Heterodienophiles have been extensively used in the synthesis of six-membered heterocycles, but extension of the reaction to nitrogen-containing dienes, particularly 2-azadienes, has received much less attention, probably owing to the lack of general methods of synthesis of these azadiene derivatives.²

Recently we reported³ a simple procedure for the preparation of unfunctionalized 2-azadienes of type (1) and shown their ability to participate as dienes in [4 + 2] cycloadditions with simple aldehydes of type (2)^{1,4} (Scheme 1). This is in contrast to reports that 2-azadienes need to be activated with electron-donor substituents in order to react with electron-poor dienophiles.^{2,5} Mariano and co-workers⁶ have reported that electronically neutral 2-azadienes undergo Lewis acid-catalysed cycloadditions to electron-rich alkenes (enol ethers and enamines) in 5–33% yields. These workers⁶ and others^{5,7} have agreed that this type of 2-azadiene fails to react with normal dienophiles; among the explanations given are conformational factors and thermal lability of the diene as well as the absence of activating substituents.

We report here the first example of a Diels–Alder reaction of electronically neutral 2-azadienes (1) with electron-poor dienophiles, *e.g.* dialkyl azodicarboxylates (3).

Thus the reaction of (1) with diethyl and di-isopropyl azodicarboxylate (3) [benzene or tetrahydrofuran (THF); 25 °C; 3–10 h] gave the Diels–Alder cycloadduct (4) as the sole stereoisomer, the yield of isolated product being higher than 85% (Scheme 1, Table 1).

Compounds (4) were characterized on the basis of their spectroscopic data and mass spectrometry.† In the absence of definitive evidence, the tentative stereochemical assignment was based on the results obtained in the reaction of (1) with aldehydes.³

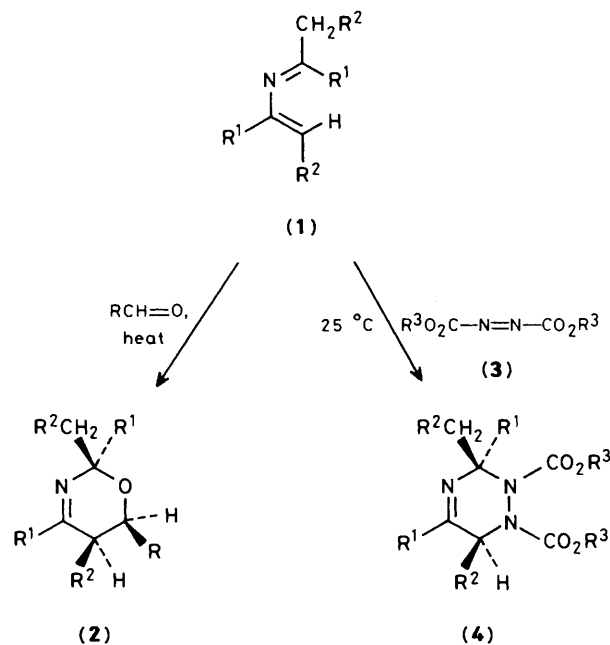
Further, when the reaction of (1) with (3) was carried out in various solvents and monitored by ¹H n.m.r. spectroscopy (90 MHz), minor reaction rate variations (*K*_{rel.} values at 15 °C for CCl₄–CD₃CN–CDCl₃ are 1 : 1.6 : 4.7) were observed as expected for a Diels–Alder reaction.⁸

When (1) was treated with isocyanates (5) (X = NR⁴, Y = O) or isothiocyanates (5) (X = NR⁴, Y = S) (benzene or THF; 80 °C; 16–60 h) cycloadducts (6) derived from the [4 + 2] cycloaddition reaction were formed in high yields (Scheme 1, Table 2). The reaction shows complete chemo- and regioselectivity.^{9–11} Thus, the ¹H n.m.r. spectrum (80 MHz, CDCl₃) of the crude reaction mixture shows for (6a), apart from the aromatic hydrogen atoms, signals at δ 0.9(t, 3H), 1.8(s, 3H), 2.3(m, 2H), and 4.5(broad, 1H, exchangeable with D₂O); the carbonyl and thiocarbonyl carbon atoms of compounds (6) appear in the ¹³C n.m.r. spectrum (20 MHz,

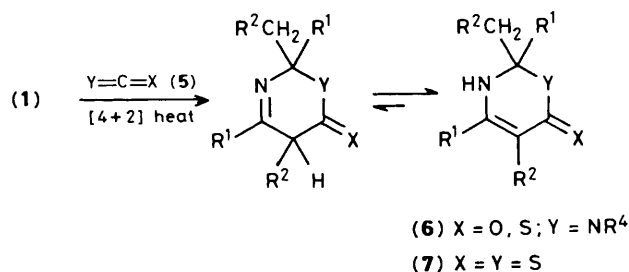
CDCl₃ or [2H₆]dimethyl sulphoxide) at *ca.* δ 170 and 191, respectively.‡

Finally, we tested the reactivity of 2-azadienes (1) towards carbon disulphide (5) (X = Y = S), whose ability to participate in [4 + 2] processes has not yet been reported,^{1a,12} and found that (1a) reacts with CS₂ in the presence of catalytic amounts of BF₃·Et₂O [molar ratio (1):CS₂:catalyst of 1 : 1.2 : 0.1] in refluxing benzene to give after 48 h the [4 + 2] cycloadduct (7a) in 50% yield (Scheme 2, Table 2).

In conclusion, the present work demonstrates the potential of unactivated 2-aza-1,3-dienes in cycloaddition reactions and their Diels–Alder reaction with electron-poor dienophiles.



Scheme 1



Scheme 2

† For example: (4c), ¹H n.m.r. (200 MHz, CDCl₃) δ 0.5(d, 3H), 0.9(t, 3H), 1.0(d, 3H), 1.25(d, 3H), 1.3(d, 3H), 1.4(d, 3H), 2.3(m, 1H), 3.3(m, 1H), 4.5(m, 1H), 5.0(m, 1H), and 5.5(q, 1H).

‡ Acid hydrolysis of (6) yielded quantitatively the expected β-oxocarboxamide or β-oxothiocarboxamide.

Table 1. 1,2,3,6-Tetrahydro-1,2,4-triazines (**4**) from 2-azadienes (**1**).

Compound ^a	R ¹	R ²	R ³	Yield/%	M.p./°C
(4a)	Ph	Me	Et	90	158—160
(4b)	Ph	Et	Et	85	120—122
(4c)	Ph	Me	Pr ⁱ	88	159—161
(4d)	<i>p</i> -MeC ₆ H ₄	Me	Pr ⁱ	89	146—148

^a All new compounds reported here gave satisfactory elemental analyses.

Table 2. 1,2-Dihydropyrimidin-4(3*H*)-ones and -thiones (**6**) and 1,2-dihydro-1,3-thiazin-6(3*H*)-thiones (**7**) from 2-azadienes (**1**).

Compound ^a	R ¹	R ²	X	Y	Yield/%	M.p./°C
(6a)	Ph	Me	O	PhN	80	163—165
(6b)	Ph	Me	O	<i>p</i> -ClC ₆ H ₄ N	75	210—212
(6c)	<i>p</i> -MeC ₆ H ₄	Me	S	PhN	82	197—199
(6d)	Ph	Me	S	<i>p</i> -MeC ₆ H ₄ N	70	194—196
(7a)	Ph	Me	S	S	50	150—152

^a All new compounds reported here gave satisfactory elemental analyses.

Financial support of this work by Comisión Asesora de Investigación Científica y Técnica (CAICYT), is gratefully acknowledged. One of us (F. J. G.) thanks Ministerio de Educación y Ciencia for a predoctoral scholarship.

Received, 24th March 1986; Com. 395

References

- For recent reviews see: (a) S. M. Weinreb and R. R. Steib, *Tetrahedron*, 1982, **38**, 3087; (b) S. M. Weinreb and J. I. Levin, *Heterocycles*, 1979, **12**, 949; S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, 1962, **62**, 405; W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876.
- D. L. Boger, *Tetrahedron*, 1983, **39**, 2869.
- J. Barluenga, J. Joglar, S. Fustero, V. Gotor, C. Krüger, and M. J. Romão, *Chem. Ber.*, 1985, **118**, 3652.
- For recent publications on Lewis acid-catalysed cycloadditions of aldehydes see: S. J. Danishefsky, E. Larson, D. Askin, and N. Kato, *J. Am. Chem. Soc.*, 1985, **107**, 1246; S. J. Danishefsky, W. H. Pearson, D. F. Harvey, C. J. Maring, and J. P. Springer, *ibid.*, p. 1256; S. J. Danishefsky and C. J. Maring, *ibid.*, **107**, p. 1269.
- F. Sainte, B. Serckx-Poncin, A.-M. Hesbain-Frisque, and L. G. Ghosez, *J. Am. Chem. Soc.*, 1982, **104**, 1428; R. Gompper and U. Heinemann, *Angew. Chem.*, 1981, **93**, 296; Y. Nomura, Y. Takeuchi, S. Tomoda, and M. M. Ito, *Chem. Lett.*, 1979, 187; M. M. Ito, Y. Nomura, Y. Takeuchi, and S. Tomoda, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 641.
- Y. S. Cheng, E. Ho, P. S. Mariano, and H. L. Ammon, *J. Org. Chem.*, 1985, **50**, 5678 and references cited therein.
- S. D. Worley, K. G. Taylor, B. Venugopalan, and M. S. Clark, *Tetrahedron*, 1978, **34**, 833; Y. M. Malécot, J. L. Ripoll, and A. Thuillier, *J. Chem. Res. (S)*, 1983, 86; (M), 1983, 959.
- J. Sauer and R. Sustmann, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 779.
- I. Matsude, K. Itoh, and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1678; I. Matsude, S. Yamamoto, and Y. Ishii, *ibid.*, 1976, 1523, 1528.
- See, R. Ritcher and H. Ulrich, p. 619—818, and L. Drobica, P. Kristián, and J. Augustin, p. 1003—1221, in 'The Chemistry of Cyanates and their Thio Derivatives,' ed. S. Patai, Part 2, John Wiley & Sons, 1977.
- R. Gompper and U. Heinemann, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 216; R. Gompper and U. Heinemann, *ibid.*, 1980, **19**, 217.
- M. Yokoyama and T. Imamoto, *Synthesis*, 1984, 798.