(4+2)-CYCLOADDITION OF NITROALKENES WITH YNAMINES;
 FORMATION OF A 4H-1,2-OXAZINE 2-OXIDE DERIVATIVE

M.L.M. Pennings and D.N. Reinhoudt*

(Laboratory of Organic Chemistry,
 Twente University of Technology, Enschede, The Netherlands)

Abstract: The formation of a thermally unstable (4+2)-cycloadduct, a 4H-1,2-oxazine 2-oxide derivative (1), from the reaction of 1-nitrocyclopentene with 1-phenyl-2-(1-pyrrolidinyl)acetylene has been proven by the structure elucidation of isoxazole derivative 3 which results from thermal rearrangement and by the structure determination of the 1,3-dipolar adducts 2 of 1 with electron-deficient acetylenes.

Although the formation of 4H-1,2-oxazine 2-oxides has been reported by Stetter and Hoehne¹, the proposed structure was after a period of confusion^{2,3} proven to be incorrect by an X-ray analysis⁴. The only six-membered cyclic nitronic esters that are known are 5,6-dihydro-4H-1,2-oxazine 2-oxides^{5,6}. In this paper we describe such a hitherto unknown 4H-1,2-oxazine 2-oxide derivative from the reaction of 1-nitrocyclopentene with 1-phenyl-2-(1-pyrrolidinyl)acetylene. Contrary to Nielsen and Archibald⁵ who have stated that an ynamine failed to react with 1-phenyl-2-nitropropene, we have recently found that nitroalkenes undergo a facile reaction with ynamines to yield both 3-nitrocyclobutenes and nitrones^{7,8}. The formation of the nitrones was accounted for by a two-step process: (4+2)-cycloaddition to yield a 4H-1,2-oxazine 2-oxide and subsequent ring contraction⁹.

1-Nitrocyclopentene and 1-phenyl-2-(1-pyrrolidinyl)acetylene react in light petroleum at room temperature to yield in addition to a nitrobicyclo[3.2.0]hept-6-ene another 1:1 reaction product (35%, MS: M^+ 284.15 ($C_{17}H_{20}N_2O_2$)). IR(KBr): 1640 cm^{-1} ($C=N$ and $C=C$). UV: λ_{max} 230 nm¹⁰. Attempts to purify the crude product failed because of its thermal instability. Even in the crystalline state or in chloroform solution at room temperature it isomerises almost quantitatively to 3-phenyl-3-(1-pyrrolidinylcarbonyl)-3a,4,5,6-tetrahydro-3H-cyclopent[*c*]isoxazole 3 (scheme 1),

m.p. 109.5-110.5°C (white crystals from light petroleum). MS: M^+ 284.15 ($C_{17}H_{20}N_2O_2$). IR(KBr): 1640 cm^{-1} (C=N and C=O). 1H NMR δ ($CDCl_3$): 2.6-2.9 and 3.2-3.6 (m, 4H, CH_2-N), 4.91 (dd, J_1 11Hz, J_2 8Hz, 1H, H-3a), 7.2-7.5 (m, 5H, H_{arom}) ppm. ^{13}C NMR data of 3 were compared with those of N,N-diethyl-3,3a-dihydro-3-methylbenzofuro[3,2-*c*]isoxazole-3-carboxamide 8, which was obtained from the reaction of 3-nitrobenzo[*b*]furan with 1-diethylaminopropyne (see table); the structure of 8 was elucidated by X-ray analysis¹¹.

The formation of 3 can be explained, assuming the initial product of the reaction between 1-nitrocyclopentene and 1-phenyl-2-(1-pyrrolidinyl)acetylene is the 4H-1,2-oxazine 2-oxide derivative 1. Homolytic cleavage of the weak N-O bond in 1 gives the diradical 2. Similar diradicals react further by the formation of a C-N bond to give 2,3-dihydro-azete 1-oxides like 6a⁷. However in the case of the fused 4H-1,2-oxazine 2-oxide derivative 1, this would lead to the nitrone 6b which has a bridgehead sp^2 -hybridized carbon atom in a four-membered ring. Consequently 2 reacts by formation of a C-O bond to yield the isoxazole derivative 3 (see also ref. 11).

Further support for structure 1 has been obtained from the identification of the reaction products of the 1,3-dipolar additions¹² of 1 with electron-deficient acetylenes. Reaction of 1 with dimethyl acetylenedicarboxylate or methyl propiolate in chloroform solution at room temperature afforded the cycloadducts 5 (scheme 2)¹³.

Since the bridgehead carbon atom in the intermediates 4 is no longer sp^2 -hybridized, ring contraction to 5 no longer leads to the formation of an anti-Bredt type of compound like 6b. The tricyclic products 5a and 5b were obtained as white solids in 83 and 85% yield respectively; 5a: m.p. 140-142°C (from benzene/hexane). MS: M^+ 426.18 ($C_{23}H_{26}N_2O_6$). IR(KBr): 1755 and 1715 cm^{-1} (COOCH₃), 1640 and 1660 cm^{-1} (C=C and C=O). 1H NMR δ ($CDCl_3$): 3.1-3.6 (m, 4H, CH_2-N), 3.76 and 3.88 (s, 3H, O-CH₃), 4.66 (dd, J_1 8Hz, J_2 1Hz, 1H, H-3a), 6.7-7.0 (m, 1H, $o-H_{arom}$), 7.1-7.5 (m, 3H, H_{arom}), 7.8-8.1 (m, 1H, $o-H_{arom}$) ppm. 5b: m.p. 124-126°C (from light petroleum). MS: M^+ 368.17 ($C_{21}H_{24}N_2O_4$). IR(KBr): 1730 cm^{-1} (COOCH₃) and 1630 cm^{-1} (C=C and C=O). 1H NMR δ ($CDCl_3$): 3.2-3.6 (m, 4H, CH_2-N), 3.80 (s, 3H, O-CH₃), 6.00 (s, 1H, H-8), 6.7-7.0 (m, 1H, $o-H_{arom}$), 7.1-7.6 (m, 3H, H_{arom}), 7.9-8.2 (m, 1H, $o-H_{arom}$) ppm. The formation

of 5a and 5b occurs stereospecifically and from the nonequivalence of the ortho-phenyl protons in the ^1H NMR spectra can be concluded, that the phenyl ring and the cyclopentane ring are on the same side of the azetidine ring. A molecular model shows that in this configuration of 5 the rotation around the $\text{C}_6\text{H}_5\text{-C-4}$ bond is restricted. The structures of 5a and 5b were also confirmed by comparison of the ^{13}C NMR data of 5a and 5b with those of dimethyl 1,6a-dihydro-1,2-diphenyl-6a-methyl-2-(1-pyrrolidinylcarbonyl)-2*H*-azeto[1,2-*b*]isoxazole-5,6-dicarboxylate 7 (see table). For this purpose compound 7 has been prepared by 1,3-dipolar addition of dimethyl acetylenedicarboxylate with the cyclic nitron 6a⁷. After 18 hours stirring in chloroform solution at room temperature, 7 was isolated as a white solid, m.p. 142-144°C. MS: M^+ 476.19 ($\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_6$). IR(KBr): 1755 and 1715 cm^{-1} (COOCH_3), 1650 cm^{-1} (C=O and C=C). ^1H NMR $\delta(\text{CDCl}_3)$: 1.25 (s, 3H, CH_3), 3.58 and 3.79 (s, 3H, O-CH_3), 5.19 (s, 1H, H-1), 7.1-7.9 (m, 10H, H_{arom}) ppm.

Table

Characteristic ^{13}C NMR absorptions of compounds <u>3</u> , <u>5a</u> , <u>5b</u> , <u>7</u> and <u>8</u>									
<u>3</u>		<u>8</u>		<u>5a</u>	<u>5b</u>		<u>7</u>		
94.4	C-3	94.6	C-3	153.3	147.1	C-7	152.9	C-5	
63.2	C-3a	96.6	C-3a	110.1	112.4	C-8	115.4	C-6	
167.4	C-6a	167.3	C-8b	82.1	81.4	C-8a	76.5	C-6a	
171.2	C=O	169.8	C=O	50.9	51.9	C-3a	51.6	C-1	
				84.7	85.1	C-4	82.6	C-2	
				165.5	166.5	>N-C=O	167.7	>N-C=O	
				161.8	158.6	-O-C=O	162.1	-O-C=O	
				159.1		-O-C=O	158.1	-O-C=O	

All chemical shifts were recorded in deuteriochloroform with TMS as internal standard (δ in ppm)

Acknowledgement. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

References and notes

1. H. Stetter and K. Hoehne, Chem. Ber., **91**, 1344 (1958).
2. A.T. Nielsen and T.G. Archibald, Tetrahedron, **25**, 2393 (1969).
3. H.O. Larson, T.-C. Ooi, A.K.Q. Siu, K.H. Hollenbeak and F.L. Cue, Tetrahedron, **25**, 4005 (1969).
4. G.B. Ansell, D.W. Moore and A.T. Nielsen, J. Chem. Soc. (B), **1971**, 2376.
5. A.T. Nielsen and T.G. Archibald, Tetrahedron, **26**, 3475 (1970).
6. G. Pitacco and E. Valentin, Tetrahedron Lett., **1978**, 2339
7. A.D. de Wit, M.L.M. Pennings, W.P. Trompenaars, D.N. Reinhoudt, S. Harkema and O. Nevestveit, J. Chem. Soc. Chem. Commun., **1979**, 993.
8. D.N. Reinhoudt and C.G. Kouwenhoven, Recl. Trav. Chim. Pays Bas, **95**, 67 (1976).
9. In our first paper⁸ the formation of N-heteroaryl-C-carbamoyl nitrones was attributed to a two-step process involving a (2+2)-cycloaddition of the ynamine to the N=O bond of the nitro group.
10. Dilute solutions of this product were studied by ¹H and ¹³C NMR spectroscopy, but the presence of radical species made this impossible. In the case of ¹³C NMR only minor amounts of rearranged product 3 could be traced.
11. See preceeding paper.
12. A.T. Nielsen in 'The Chemistry of the nitro and nitroso groups', ed. H. Feuer, J. Wiley & Sons, New York, 1969; part I, p. 349.
13. The isoxazole derivative 3 failed to react with dimethyl acetylenedicarboxylate under the same reaction conditions.

(Received in UK 4 March 1980)