

CYANOKETENES. STEREOCHEMISTRY OF THE 2-AZETIDINONES RESULTING FROM THE CYCLOADDITIONS OF CYANOKETENES TO FORMIMIDATES

Richard Chambers, Donna Kunert, Louis Hernandez, Jr., Frank Mercer, and Harold W. Moore

Department of Chemistry, University of California, Irvine, California 92717

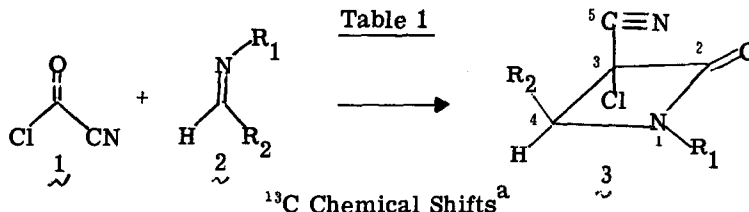
(Received in USA 19 November 1977; received in UK for publication 23 January 1978)

In the preceding paper¹ a synthetic route to chloro-, bromo-, and iodocyanoketene was described along with the ability of these halocyanoketenes, as well as some typical alkylcyanoketenes (tert-butyl- and methyl), to undergo stereospecific cycloadditions to formimidates to give 2-azetidinones. Reported here are data which show the stereochemistry of these adducts to be that in which the 3-cyano- and 4-protio groups reside in a trans relationship.

For those 2-azetidinones arising from the cycloadditions of halocyanoketenes, cmr spectroscopy has proven most useful for determination of the stereo structures. The assignments of the individual ¹³C chemical shifts have been made by consideration of the relative peak intensities, off-resonance decoupling techniques, and the comparison of spectra of compounds containing closely related structural units. A summary of the pertinent ¹³C chemical shift data for the 2-azetidinones, 3a-m, is tabulated in Table 1. It is noteworthy that the cyano absorption (C-5) in 3a-m does not vary by more than 0.3 ppm from 111.6 ppm. This observation is consistent with the assumption that these 2-azetidinones all have the same configuration.

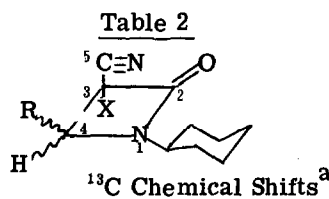
In view of the invariance of the cyano absorption, we chose to investigate the possibility of using the ¹³C chemical shift of this group as a stereochemical probe. To this end, the ¹³C spectra of compounds 3c, 4a, 6a, 6b, 8a, and 8b were examined. These compounds were prepared as outlined below and their pertinent cmr data are presented in Table 2.

Silica gel chromatography of 4a and 8a gave samples which were enriched in the E-isomers as determined by the magnitude of the coupling constants of the C-3 and C-4 methine protons in the respective isomers.² From these data it is possible to unambiguously assign the up-field cyano resonance to the Z-isomer, respectively, 113.4 ppm vs 113.8 ppm for 4a and 112.5 ppm vs 113.1 ppm for 8a. It is anticipated that the relative positions of the cyano absorptions in the E- and Z-isomers of 3c, 6a, 6b, and 8b should be the same as those for the respective isomers of 4a and 8a since a change in the substituent at C-3 (i.e., E-4a → Z-6a



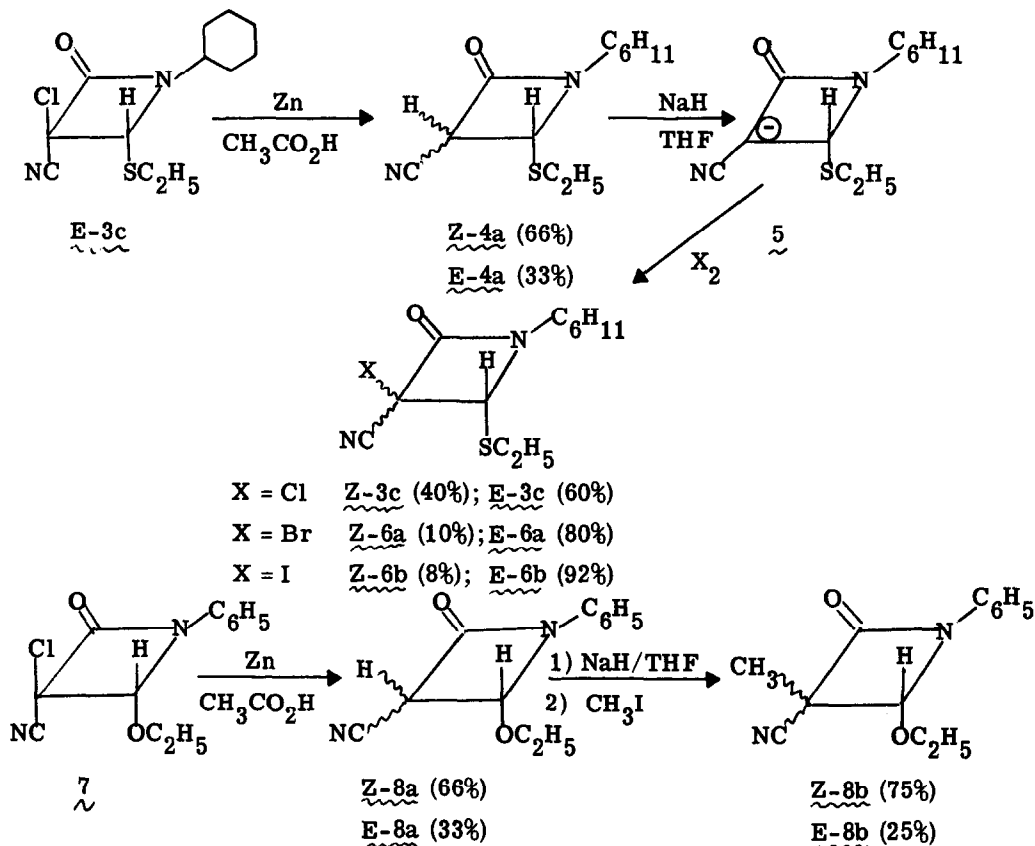
	R ₁	R ₂	Yield	C-2 ppm	C-3 ppm	C-4 ppm	C-5 ppm		R ₁	R ₂	Yield	C-2 ppm	C-3 ppm	C-4 ppm	C-5 ppm
a	C ₆ H ₁₁	OEt	94	154.3	60.2	90.0	111.3	h	C ₆ H ₅	S Me	70	152.7	61.9	70.5	111.3
b	C ₆ H ₁₁	S Me	85	155.0	61.8	71.0	111.8	i	C ₆ H ₅	S Et	46	152.7	62.8	71.1	111.4
c	C ₆ H ₁₁	S Et	78	154.9	62.7	71.3	111.9	j	C ₆ H ₅	S i-Pr	56	152.7	63.4	70.7	111.5
d	C ₆ H ₁₁	S i Pr	50	154.4	62.9	69.8	111.8	k	C ₆ H ₅	S n-Bu	72	152.7	62.7	71.3	111.4
e	C ₆ H ₁₁	S n-Bu	82	154.3	62.5	70.9	111.7	l	C ₆ H ₅	S t-Bu	56	152.5	63.3	69.8	111.6
f	C ₆ H ₁₁	S t-Bu	67	155.0	68.7	68.8	111.9	m	C ₆ H ₅	S Ph	36	152.6	62.9	73.8	111.5
g	C ₆ H ₁₁	S Ph	47	154.4	62.5	73.4	111.8								

(a) In ppm downfield from TMS



	X	R	Isomer	C-2	C-3	C-4	C-5
4a	H	SEt	E	156.0	60.1	45.7	113.8
			Z	156.7	58.5	46.7	113.4
3c	Cl	SEt	E	154.9	62.7	71.2	111.9
			Z	157.8	57.6	67.8	113.5
6a	Br	SEt	E	155.1	47.0	71.0	112.3
			Z	155.1	50.3	69.7	114.0
6b	I	SEt	E	156.5	16.5	71.2	114.2
			Z	156.2	15.7	67.6	115.6
8a	H	OEt	E	155.4	62.9	82.2	113.1
			Z	156.3	64.0	79.7	112.5
8b	CH ₃	OEt	E	160.6	65.6	85.9	117.7
			Z	160.5	64.9	87.4	116.0

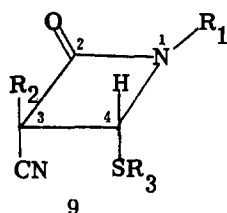
(a) In ppm downfield from TMS



and $\text{Z-4a} \rightarrow \text{E-6a}$) should, in an electronic sense, have an equal effect on both transformations. If this is indeed the case, then the E- and Z-isomers of 3c , 6a , 6b , and 8b can be assigned on the basis of their C-5 cyano absorption as shown in Table 2. This also allows us to assign the E-stereochemistry to the 2-azetidinones, 3a-m , based upon the relationship between the C-5 cyano absorption of these compounds (Table 1) and the respective cyano absorptions for the E- and Z-isomers of 3c (Table 2).

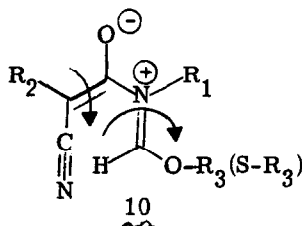
As shown in the preceding paper, alkylcyanoketenes (*tert*-butyl- and methyl-) also add stereospecifically to formimidates. It can now be shown that the resulting 2-azetidinones also have stereochemistry analogous to that for 3a-m , i.e., 3-alkyl *cis* to 4-proton. For example, NOE (Nuclear Overhauser Effect) experiments were carried out on 9a-d . Irradiation of the C-3 methyl absorption in 9a and 9b , and the C-3 *tert*-butyl absorption in 9c and 9d caused a respective increase of 22%, 16%, 22%, and 27% in the integrated intensity of the C-4 methine proton absorption. Also, as mentioned, 1 methylation (CH_3I) of the anion 5 gives a product identical in all respects to 9a . Thus, this alkylation must take place from the side opposite the $\text{-CH}_2\text{CH}_3$ group.⁴ Therefore, one can reasonably assume that the major products resulting from halogenation of 5 , i.e., E- 3c , E- 6a , and E- 6b , along with those products arising from the acylation,

aldol condensation, and Michael addition of **5** also have the 3-cyano and 4-protio groups in a trans relationship.



	R_1	R_2	R_3	NOE (C-4 proton intensity enhancement)
a)	C_6H_{11}	CH_3	CH_3	22%
b)	C_6H_5	CH_3	C_6H_5	16%
c)	C_6H_{11}	$C(CH_3)_3$	CH_3	22%
d)	C_6H_5	$C(CH_3)_3$	C_6H_5	27%

Finally, it is of particular significance to point out that all cyanoketene/formimidate cycloadditions studied give 2-azetidinones having analogous stereochemistry, and that this is completely independent of the steric bulk of the ketene. Since the observed stereochemistry is counter to that expected if the cycloaddition were a concerted $\pi 2s + \pi 2a$ reaction, we suggest that these cyanoketene cycloadditions proceed via the zwitterion, **10**, and that this undergoes the indicated conrotatory ring closure to the observed 2-azetidinones. The high stereospecificity of these cycloadditions may result from a unique feature of the cyanoketenes. That is, we suggest that the cyano group prefers to reside in the indicated endo position of the zwitterion since it accommodates some of the negative charge density of the anion. As a result, when endo, it experiences some electrostatic attraction to the iminium ion. On steric grounds, the endo proton on the iminium ion is clearly preferred over the alkoxy group.



References and Notes

1. D. Kunert, R. Chambers, F. Mercer, L. Hernandez, and H. W. Moore, Tetrahedron Lett., preceding article.
2. E-isomer, $J_{H_3-H_4} = 1.5$ Hz; Z-isomer, $J_{H_3-H_4} = 5.0$ Hz. See K. D. Banrow and T. M. Spotswood, ibid., 3325 (1965).
3. It should be noted that no attempt has been made to assess any contribution due to steric compression in the Z-isomers of **3c**, **6a**, **6b**, and **8b**.
4. Note that methylation of **8** via its anion is not stereospecific. This difference between the the oxygen and sulfur series is not as yet clear.
5. The authors wish to thank the National Science Foundation (CHE-06932) for financial support.