UC Irvine

UC Irvine Previously Published Works

Title

Cyanoketenes. Synthesis and cycloadditions to formimidates

Permalink

<https://escholarship.org/uc/item/62v8w96j>

Journal

Tetrahedron Letters, 19(11)

ISSN

0040-4039

Authors

Kunert, DM
Chambers, R
Mercer, F
et al.

Publication Date

1978

DOI

10.1016/S0040-4039(01)85417-4

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

CYANOKETENES. SYNTHESIS AND CYCLOADDITIONS TO FORMIMIDATES

Donna M. Kunert, Richard Chambers, Frank Mercer, Louis Hernandez, Jr., 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)

We have previously reported that β -azido- α -chloro- γ -methoxy- $\Delta^{\alpha, \beta}$ -crotonolactone (1a) undergoes thermolysis in refluxing benzene to give chlorocyanoketene (2a) and methylformate.¹ Reported here is the observation that the corresponding α -bromo- and α -iodo-analogs of 1 undergo analogous thermolyses to give the respective halocyanoketenes, 2b and 2c. In addition, it is reported that these halocyanoketenes, 2a-c, as well as tert-butyl-, 2d, and methylcyanoketene, 2e,² readily undergo stereospecific cycloadditions to a variety of formimides to give 2-azetidinones (β -lactams), 4a-z.

The β -azido- α -halo- γ -methoxy- $\Delta^{\alpha, \beta}$ -crotonolactones, 1b,c, were prepared in high yields from the corresponding mucohalic acids³ by the general procedure previously reported for the synthesis of 1a.¹ These azidobutenolides along with the appropriately substituted 2,5-diazido-1,4-benzoquinones,² e.g., 2,5-diazido-3,6-dimethyl-, 3e and 2,5-diazido-3,6-di-tert-butyl-1,4-benzoquinone, 3d, provide the best known precursors to a variety of substituted cyanoketenes. In view of the renewed interest in the synthesis and biological activity of monocyclic β -lactams, a detailed study of the cycloadditions of chloro-, bromo-, iodo-, methyl-, and tert-butylcyanoketene to formimides was accomplished. The salient result of this study is the observation that these cyanoketenes undergo stereospecific cycloaddition to a wide variety of formimides and thioformimides to give 2-azetidinones in which the 3-cyano and the 4-protio groups reside in a trans arrangement, i.e., 4a-z. In addition, 4d was used as a model and converted to the anion, 6, which reacts stereospecifically with a variety of electrophiles to give 2-azetidinones having further elaboration at position -3, i.e., 7a-i.

For the halocyanoketenes, the cycloadditions were accomplished by refluxing a solution containing 1.0 equivalent of the β -azido- α -halo- $\Delta^{\alpha, \beta}$ butenolides, 1a-c, and 1.1 equivalents of the appropriate formimide for several hours. For the alkylcyanoketenes, 3d,e, a benzene and chlorobenzene solution, respectively, containing 0.5 equivalents of the 2,5-diazidoquinone was slowly added to a refluxing benzene solution containing 1.1 equivalents of the formimide. After an additional hour the solvent was removed in vacuo and the product purified by chromatography or recrystallization. The yields reported for the 2-azetidinones, 4a-z, are those obtained for the puri-

4	mp	yield	X	R ₁	R ₂	mp	yield	X	R ₁	R ₂
a	oil	94	Cl	C ₆ H ₁₁	-OEt	n	oil	72	Cl	C ₆ H ₅ -SnBu
b	oil	85	Br	C ₆ H ₁₁	-OEt	o	oil	56	Cl	C ₆ H ₅ -S-tBu
c	oil	66	I	C ₆ H ₁₁	-SEt	p	oil	36	Cl	C ₆ H ₅ -SPh
d	oil	78	Cl	C ₆ H ₁₁	-SEt	q	oil	40	Me	C ₆ H ₁₁ -SMe
e	oil	63	Br	C ₆ H ₁₁	-SEt	r	oil	50	Me	C ₆ H ₁₁ -SEt
f	oil	85	Cl	C ₆ H ₁₁	-SMe	s	117-19	28	Me	C ₆ H ₁₁ -S-tBu
g	oil	50	Cl	C ₆ H ₁₁	-SiPr	t	oil	80	Me	C ₆ H ₅ -SEt
h	oil	82	Cl	C ₆ H ₁₁	-SnBu	u	oil	59	Me	C ₆ H ₅ -SPh
i	oil	67	Cl	C ₆ H ₁₁	-StBu	v	118-19	35	t-Bu	C ₆ H ₁₁ -S-Me
j	oil	47	Cl	C ₆ H ₁₁	-SPh	w	81-82	29	t-Bu	C ₆ H ₁₁ -SnBu
k	oil	70	Cl	C ₆ H ₅	-SMe	x	173-75	34	t-Bu	C ₆ H ₁₁ -S-tBu
l	oil	46	Cl	C ₆ H ₅	-SEt	y	127-28	20	t-Bu	C ₆ H ₅ -SEt
m	oil	56	Cl	C ₆ H ₅	-SiPr	z	108-09	31	t-Bu	C ₆ H ₅ -SPh

fied products and no attempts were made to maximize. However, pmr analysis of the crude reaction products showed that these β -lactams were generally formed in >80% yield and only one isomer could be detected. The pmr, cmr, ir, mass spectra and/or analytical properties are all in strict accord with their indicated formulations. The stereochemistry as represented by structure 4 has been unambiguously established for a number of these compounds. These data are presented in the accompanying manuscript.

A noteworthy observation, which will be reported in detail subsequently, is that many of these β -lactams show marked antibiotic as well as antifungal activity. Thus, we had a desire for additional synthetic methodology which would expand the versatility of the cycloaddition

route and allow the construction of still further examples of potentially active β -lactams. To this end, an investigation to further elaborate the cyano- β -lactam ring system was initiated. Specifically, we envisaged that anions such as **6** would function as powerful synthetic precursors to a wide variety of substituted 2-azetidinone derivatives. We now report that this anion, **6**, can be generated in greater than 85% yield by an initial reductive dechlorination ($\text{Zn}/\text{CH}_3\text{CO}_2\text{H}$) of **4d** to give the dihydro derivative **5**,⁴ which upon treatment with NaH/THF at 0° gives the anion **6**. Significantly, this anion undergoes stereospecific alkylation, acylation, aldol condensation and Michael addition, and representative examples are given below. Again, only one isomer was detected,⁵ and it is assumed that these arise via attack of the electrophile from the side opposite the $-\text{SCH}_2\text{CH}_3$ group. This is, in fact, certainly true for the alkylation with methyl iodide since the product is identical to that formed when methylcyanoketene cycloadds to N-cyclohexyl-S-ethylthioformimidate, and the stereochemistry of this adduct has been established (see following manuscript).

E^+		E	Yield	mp
a)	CH_3I	CH_3-	91	oil
b)	$\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$	$\text{CH}_2=\text{CH}-\text{CH}_2-$	59	oil
c)	CH_3COCl	$\text{CH}_3\text{CO}-$	29	oil
d)	$\text{C}_6\text{H}_5\text{COCl}$	$\text{C}_6\text{H}_5\text{CO}-$	43	oil
e)	CH_3OCOCl	$\text{CH}_3\text{OCO}-$	90	$65-66^\circ$
f)	$\text{C}_6\text{H}_5\text{CHO}$	$\text{C}_6\text{H}_5-\underset{\text{OH}}{\text{CH}}-$	60	$127-129^\circ$
g)	$(\text{CH}_3)_3\text{-C-N=O}$	$(\text{CH}_3)_3\text{-C-NH-CO}-$	72	$63-65^\circ$
h)	$\text{CH}_2=\text{CH}-\text{CN}$	$\text{NC-CH}_2\text{CH}_2-$	63	$41-42^\circ$
i)	$\text{CH}_2=\text{CH-COCH}_3$	$\text{CH}_3\text{CO-CH}_2\text{-CH}_2-$	92	oil

In conclusion, we wish to emphasize that the cyanoketene cycloadditions and β -lactam anion chemistry reported here, in conjunction with our previously related report that β -azido-pyrrolinones ring contract to β -lactams,¹ constitutes perhaps the best synthetic route to highly substituted monocyclic 2-azetidinones.

References and Notes

1. H. W. Moore, L. Hernandez, Jr. and A. Sing, J. Am. Chem. Soc., **98**, 3728 (1976).
2. W. Weyler, W. Duncan, and H. W. Moore, ibid., **97**, 6187 (1975).
3. Mucobromic acid is commercially available, while β -chloro- α -iodo- γ -hydroxy- $\Delta^{\alpha, \beta}$ -crotonolactone was prepared by the method of E. Beška and P. Rapoš, J. Chem. Soc., Perkin I, 2470 (1976). The spectral and analytical properties of all new compounds reported here are in agreement with their indicated formulations.
4. The β -lactam, **5**, thus formed was obtained as a mixture of the cis and trans isomers in a ratio of 2:1, respectively. The stereochemistry was readily assigned on the basis of the coupling constants for the methine protons. See, K. D. Banrow and T. M. Spotswood, Tetrahedron Lett., 3325 (1965).
5. Actually two diastereomers were observed from the aldol product **7f**. However, these are due to the difference in chirality at the carbinol carbon.
6. The authors wish to thank the National Science Foundation (CHE-06932) for financial support.