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CYANOKETENES. CYCLOADDITIONS OF CHLOROCYANOKETENE TO α,β -UNSATURATED IMINES

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Summary Chlorocyanoketene cycloadds to cinnamylideneamines to give β -lactams, δ -lactams, and pyridones. The periselectivity and stereoselectivity of these cycloadditions is markedly influenced by the N-substituent as well as the β -substituents of the imines.

Reported here is an investigation of the cycloadditions of chlorocyanoketene (CCK) to α,β -unsaturated imines. Based upon previous work,¹ these cycloadditions were anticipated to proceed via a dipolar (zwitterion) mechanism and thus, with unsaturated imines, both β - and δ -lactams were anticipated. This was, in fact, observed. However, our primary goal was to determine those factors which would maximize the formation of β -lactams of the general structure 1, since such compounds would provide reagents for the construction of a large variety of monocyclic β -lactams.² For example, reductive dechlorination would give the corresponding 3-cyano-2-azetidiones which are easily functionalized via their enolate anions.³ Additionally, oxidative cleavage of the alkenyl group would result in a 4-formyl-2-azetidione and thus allow further modifications via the aldehyde group.⁴ The results described here meet the cycloaddition objectives, and further-

more, do so in such a fashion as to allow complete control of stereochemistry at positions -3 and -4. Depending upon R_1 and R_2 exclusively the E- or Z-isomers of 1 can be obtained.

A slight excess of CCK (1.1 eq) was generated from the thermolysis of 4-azido-3-chloro-5-methoxy-2(2H)-furanone³ in refluxing benzene in the presence of 1 eq of the imines 2a-f. These imines were chosen so that the steric bulk of both the N-substituent as well as the β -position were systematically varied. The observed results are outlined in Scheme 1. The most significant points of this study are the following: 1) The selectivity for β -lactam formation is low in the cinnamylideneamine series 2a-c. However, formation of the E-isomer 3c starts to effectively compete as the N-substituent is reduced in steric bulk. 2) Remarkably high selectivity for β -lactam formation is observed for imines 2d,f. Exclusively the Z-isomer, 4d, is formed from the N-t-butyl imine and only the E-isomer 3f results from the N-p-methoxyphenyl analog. The N-cyclohexyl imine 2e, having an intermediately sized N-substituent, gave a mixture of both β -lactams 3e,4e as well as the δ -lactam, 5e.

Scheme 1

The structures of the products are based upon spectral (Table 1), analytical, and chemical evidence. The E-stereochemistry for 5a-c was assigned on the basis of their failure to undergo dehydrohalogenation ($(\text{C}_2\text{H}_5)_3\text{N}$) to the respective pyridones. The stereochemistry of the β -lactams 3c, 4d, and 3f was assigned on the basis of the following chemical transformations. They were each dehalogenated ($\text{Zn}/\text{CH}_3\text{CO}_2\text{H}$) and the resulting β -lactams converted to their enolates (NaH/THF).⁵ Treatment of the enolates from 3c,f with N-chlorosuccinimide regenerated the initial 3-chloro-2-azetidinones as the major diastereomer. For the Z-isomer, 4d, its diastereomer 7 was the major product. Thus, assuming that chlorination of the enolates takes place from the least hindered face allows the stereochemical assignments as indicated for 3c, 4d, and 3f. Stereochemical assignment of 3e and 4e was made directly from their NMR spectra. That is, it has previously been shown that the proton at C_4 in 3-cyano-2-azetidinones experiences a greater deshielding when cis to the 3-cyano group than when trans.⁶ The assigned stereostructures for 3e and 4e are consistent since the chemical shift of this proton in the former appears at δ , 4.32 and the latter at δ , 4.61.

Detailed mechanistic discussions as well as further synthetic applications will be presented subsequently. At this time suffice it to say that zwitterions 8 and 9 are viewed as the direct precursors to, respectively, 3f and 4d and give such upon conrotatory ring closure.

If $R = t\text{-C}_4\text{H}_9$, zwitterion 8 controls product (4d) formation since steric interaction $a < b$. For $R = \text{C}_6\text{H}_4\text{OCH}_3$ the opposite is true and 9 leads only to 3f. It is noteworthy that analogous arguments using steric interaction a) and b) can be invoked to explain a variety of other ketene/imine cycloadditions.

Table 1 ⁷
Spectral Data

Compound	mp	$\nu_{\text{C=O}}$ $\nu_{\text{C=N}}$	NMR (CDCl_3, δ)	MW Mass Spec.
<u>3c</u>	124.5-125.5	1780	3.74 s (3); 4.79 d (1) J, 8; 6.21 d, d (1) J, 8, 15; 7.40 m (9); 7.00 d (1) J, 15	338
<u>3e</u>	not separable *	1800 2250	1.50 m (10); 3.45 m (1); 4.30 d (1) J, 10; 6.06 d (1) J, 10; 7.35 m (10)	390
<u>3f</u>	126-127	1792	3.74 s (3); 4.73 d (1) J, 10; 6.10 d (1) J, 10; 7.25 m (14)	414
<u>4d</u>	139-140	1792 2240	1.37 s (9); 4.57 d (1) J, 9; 5.94 d (1) J, 9; 7.25 m (10)	364
<u>4e</u>	not separable *	1800 2250	1.50 m (10); 3.45 m (1); 4.59 d (1) J, 10; 5.95 d (1) J, 10; 7.35 m (10)	390
<u>5a</u>	103-104	1690	1.55 s (9); 3.92 d (1) J, 6; 5.32 d, d (1) J, 6, 8; 6.62 d (1) J, 8; 7.30 m (10)	288

Compound	mp	$\nu_{\text{C=O}}$ $\nu_{\text{C}\equiv\text{N}}$	NMR (CDCl ₃ , δ)	MW Mass Spec.
5b ~	168-169	1675 2260	1.50 m (10); 4.35 m (1); 3.97 d (1) J, 6; 5.40 d,d (1) J, 6, 8; 6.43 d (1) J, 8; 7.26 m (5)	314
5c ~	141-142	1688	3.79 s (3); 4.10 d (1) J, 6; 5.45 d,d (1) J, 6, 8; 6.48 d (1) J, 8; 7.30 m (9)	338
5e ~	134-135	1690	1.50 m (10); 4.35 m (1); 5.80 d (1) J, 9; 6.20 d (1) J, 9; 7.30 m (10)	390
6a ~	180-182	1665 2275	1.70 s (9); 6.27 d (1) J, 7; 7.45 m (5); 7.78 d (1) J, 7	252
6b ~	210-211	1650 2260	1.75 m (10); 4.85 m (1); 6.35 d (1) J, 8; 7.50 m (5); 7.60 d (1) J, 8	278
6c ~	193-194	1660 2260	3.72 s (3); 6.35 (1) J, 7; 7.20 m (9); 7.48 d (1) J, 7	302

*The β -lactams 3e and 4e were not separated. However, their individual spectral data could be obtained from the ^1H nmr spectrum of the diastereomeric mixture.

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References and Notes

1. H. W. Moore, Acc. Chem. Res., 1979, **12**, 125; F. Duran and L. Ghosez, Tetrahedron Lett., 1970, 245; R. Gomper, Angew. Chem., Int. Ed., 1969, **8**, 312.
2. The recent discoveries of biologically active monocyclic β -lactams has renewed interest in these compounds. See, for example, R. B. Sykes, C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgeopapadatou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo, and J. S. Wells, Nature, 1981, 291, 489; A. Imada, K. Kitano, K. Kintaka, M. Mori and M. Asai, Nature, 1981, **298**, 590.
3. D. M. Kunert, R. Chambers, F. Mercer, L. Hernandez, and H. W. Moore, Tetrahedron Lett., 1978, 929.
4. See, for example, T. W. Doyle, B. Belleau, B. Y. Lug, C. F. Ferrari, and M. P. Cunningham, Can. J. Chem., 1977, **55**, 468.
5. For further examples see H. W. Moore, L. Hernandez, D. M. Kunert, F. Mercer, and A. Sing, J. Am. Chem. Soc., 1981, **103**, 1769.
6. R. Chambers, D. Kunert, L. Hernandez, and H. W. Moore, Tetrahedron Lett., 1978, 933.
7. Satisfactory elemental analysis was obtained for the new compounds reported here.

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