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CYCLOADDITION OF CHLOROKETENE TO IMINES: SYNTHESIS OF CIS AND TRANS 3-CHLORO-2-AZETIDINONES

David A. Nelson

Organic Chemicals Production Research
The Dow Chemical Company, Midland, Michigan 48640

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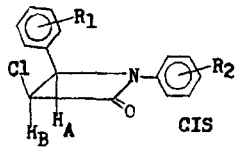
The cycloaddition of chloroketene (1), with imines has not been extensively investigated. Recently, 3-chloro-1,4-diphenyl-2-azetidinone (2) and the bromo-analog (3) were prepared by this route and a single isomer (trans) was isolated. It has generally been established that aldoketene cycloadditions yield only the trans isomer (4).

The adduct of asymmetrical ketoketenes and benzalaniline yielded both cis and trans β-lactams (5). Bulkier groups in the 3-position produced more cis isomer. To determine what conditions might lead to cis isomers, the effect of various substituents on benzalaniline was investigated. Previous substituent studies were concerned with yields rather than stereochemistry (6,7). Some substituted diaryl 3-chloro-2-azetidinones have already been prepared by other routes (8).

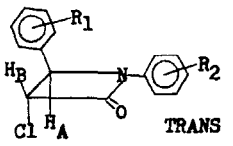
The following procedure was utilized for the synthesis of β-lactams. A solution of 0.20 mole imine and 0.21 mole triethylamine was prepared in 250 ml benzene. The solution was warmed to 70-75°, and chloroacetyl chloride (0.21 mole) was added dropwise. After two hours the mixture was cooled, filtered, washed and dried over sodium sulfate. The solvent was removed in vacuo. The residue was dissolved in methylene chloride or benzene-hexane (2:3 v/v) and applied to an alumina column. The eluting solvent was removed and the isomers were fractionally crystallized from ethanol. Attempts to prepare β-lactams with electron withdrawing groups at room temperature were unsuccessful. Consequently, all reactions were performed at the elevated temperature for a comparative basis.

Previous investigations (9,10) have shown that coupling constants of vicinal protons in monocyclic β-lactams, J(cis)> J(trans), can be used to distinguish the isomers. The range of coupling constants for the 3-chloro-2-azetidinones in this study was 1.7 to 2.0 cps

Table I. Isomer ratios, yields and nmr values[a] of some β-lactams



CIS



TRANS

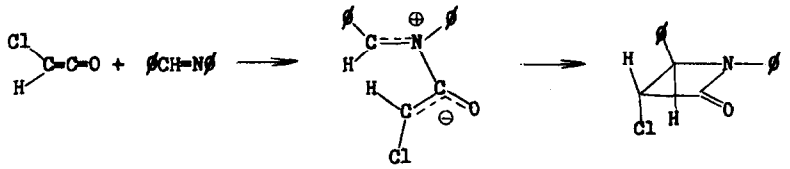
	R_1	R_2	cis/trans	yield(%)	δ_{H_A}(ppm) cis/trans	δ_{H_B}(ppm) cis/trans	J_{AB}(cps) cis/trans
I	H	H	0/100	4	4.98	4.58	2.0
II	o-nitro	p-methoxy	50/50	19	6.04/5.64	5.51/4.66	5.5/1.8
III	o-nitro	p-chloro	32/68	6	6.22/5.67	5.54/4.69	5.4/1.9
IV	o-nitro	2,4-dimethyl	22/78	9	6.28/5.85	5.44/4.72	5.3/2.0
V	o-nitro	o-bromo	20/80	2	6.68/6.24	5.56/4.78	5.4/2.1
VI	o-nitro	H	44/56	9	6.08/5.68	5.50/4.65	5.4/1.9
VII	m-nitro	p-methoxy	0/100	9	5.20	4.73	1.9
VIII	p-nitro	p-methoxy	0/100	16	5.13	4.64	1.9
IX	o-chloro	p-methoxy	18/82	30	5.59/5.49	5.28/4.59	5.2/1.9
X	o-chloro	H	13/87	28	5.72/5.48	5.30/4.57	5.2/1.9
XI	p-chloro	p-methoxy	0/100	7	4.95	4.57	1.9
XII	o-methoxy	p-methoxy	10/90	28	5.64/5.28	5.19/4.68	5.5/1.9
XIII	o-methoxy	H	0/100	25	5.32	4.71	2.0
XIV	p-methoxy	p-methoxy	0/100	65	4.92	4.57	1.9
XV	o-methyl	p-methoxy	10/90	45	5.53/5.25	5.30/4.51	5.3/2.0
XVI	o-methyl	H	0/100	20	5.28	4.51	2.0
XVII	o-t-butyl	p-methoxy	25/75	10	6.04/5.77	5.33/4.52	5.2/1.7

[a]Values are reported relative to internal TMS in $CDCl_3$

for J(trans) and 5.2 to 5.5 cps for J(cis). The isomer ratios were determined before column separation to avoid variation during purification. The p-methoxy group (R_2) was used extensively in this investigation due to its more favorable yields (7).

Two general observations are evident from the isomer ratios. An ortho R_1 group enhanced the formation of cis isomers; whereas, para or meta R_1 groups gave only trans isomers. The isomer ratio was influenced by the ortho R_1 group and the R_2 groups. The o-nitro and o-chloro series are especially significant. No cis isomer was found in preparation of XIII and XVI.

All evidence has indicated an open chain intermediate in ketene cycloadditions to imines (11). A mechanism utilizing the intermediate has been proposed for the chloroketene addition to benzalaniline (2).



Epimerization studies (3) have shown that the trans isomer was the more stable 3-bromo-2-azetidinone, with no interconversion in the presence of triethylamine.

Although the ortho R_1 groups were necessary for cis isomer formation, steric hindrance alone does not satisfy the mechanistic requirements. This is particularly obvious from the isomer ratios of II and XVII. Further evidence for this conclusion was obtained by the preparation of 3-chloro-1-(p-methoxyphenyl)-4-(2-pyridyl)-2-azetidinone. The isomer mixture was 27% cis and 73% trans with a yield of 5%. The isomer ratios of II and VIII indicate that electronic effects cannot singly account for the results. Consequently, both steric and electronic effects may be involved during the two step cycloaddition.

It is interesting that the isomer mixtures are not limited to just chloroketene adducts. The methylketene adduct, 3-methyl-1-(p-methoxyphenyl)-4-(o-nitrophenyl)-2-azetidinone was 36% cis and 64% trans (yield, 25%).

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