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CYCLOADDITION OF HALOKETENES TO IMINES : A CONVENIENT SYNTHESIS OF FUNCTIONALLY SUBSTITUTED β-LACTAMS AND 2-PYRIDONES.

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Despite constant interest in finding new and efficient routes to biologically active β-lactams, the synthesis of reactive and properly substituted β-lactams remains difficult. In connection with their work on penicillin, Sheehan and Corey (1) allowed Schiff bases to react with phtaloylglycyl- or succinylglycylchloride in the presence of triethylamine. Subsequent hydrazinolysis could convert the resulting acylamino-β-lactams to the corresponding 3-amino-β-lactams. However, this approach is very much limited by the sensitivity of many β-lactams toward hydrazine (2) . Another route involves the synthesis of 3-azido-β-lactams and their subsequent reduction but this appears unsuitable for the synthesis of penicillin derivatives having natural configuration at C_5-C_6 (3) .

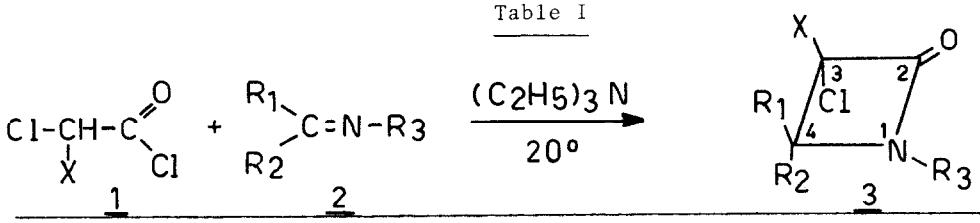
We wish to report on an extension of our work on haloketenes (4) to a simple and efficient synthesis of α-halogenated-β-lactams (5) which are potential precursors of various functionally substituted β-lactams.

The dropwise addition of 0.02 mole monochloroacetylchloride 1a (X=H) in 50 ml benzene to a solution of benzophenoneanil 2a (0.01 mole) and triethylamine (0.02 mole) at room temperature yielded quantitatively 1,4-triphenyl-3-chloro-2-azetidinone 3a . The same procedure was successfully applied for the synthesis of α-chloro- and α,α-dichloro-β-lactams (Table I) from Schiff bases derived from aromatic as well as aliphatic amines (6) .

The β-lactams have been identified by a combination of elemental and spectral (mass, i.r. and n.m.r.) analyses. It is worth noting that the reaction of monochloroacetylchloride with benzalaniline in the presence of

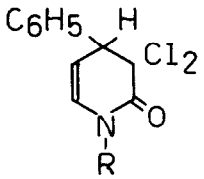
triethylamine gave a single stereoisomer **3c** having the trans-configuration at C_3-C_4.

Table I



Compound	X	R_1	R_2	R_3	Yield %	$\nu_{C=O}$ ($CHCl_3$)	δ_{H_3} ($CDCl_3$, from TMS)	δ_{H_4}
3a	H	C_6H_5	C_6H_5	C_6H_5	100	1760	5.35(s)	
3b	Cl	C_6H_5	C_6H_5	C_6H_5	100	1780	-	
3c	H	C_6H_5	H	C_6H_5	70	1765	4.60(d)	5.02(d)
3d	Cl	C_6H_5	H	C_6H_5	100	1785	-	5.33(s)
3e	Cl	C_6H_5	H	$CH_3(CH_2)_3$	70	1782	-	5.07(s)
3f	Cl	C_6H_5	H	C_6H_{11}	90	1775	-	5.07(s)

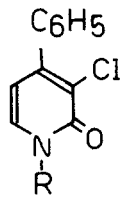
When the imine function is part of a conjugated system both 1,2 and 1,4 cycloadducts can be formed. The dehydrochlorination of dichloroacetylchloride with triethylamine in the presence of Schiff bases derived from cinnamaldehyde gave only the δ-lactams **4a-c** ($\nu_{C=O}$ 1698 cm^{-1}) which were readily converted into the corresponding α-chloro-2-pyridones **5a-c** ($\nu_{C=O}$ 1650 cm^{-1}) in an excess of triethylamine.



4 a, R= C_6H_5

b, R= $CH_3C_6H_4$

c, R= $C_6H_5CH=CH-CH=N-$



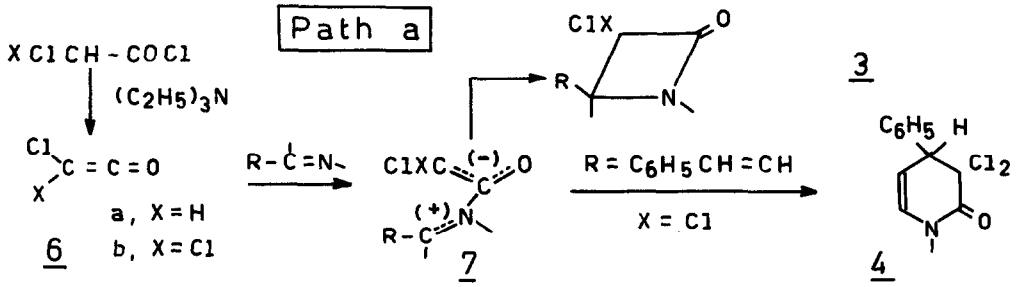
5a, R= C_6H_5 ; 45%

b, R= $CH_3C_6H_4$; 67%

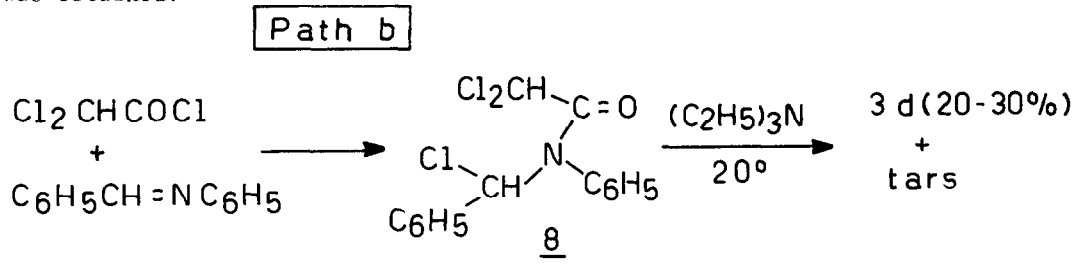
c, R= $C_6H_5CH=CH-CH=N-$; 75%

Two main interpretations are offered for the mechanistic origin of the β- and δ-lactams. The most plausible pathway involves the initial formation of

monochloro- or dichloroketene 6a,b followed by cycloaddition to the imine through a dipolar intermediate 7 which closes to form the lactam ring (7) . A higher ground state energy and a more favourable distribution of the dipole's negative charge by the chlorine substituents readily account for the increased reactivity of these chloroketenes as compared with ketene itself (8) .



Furthermore, this pathwway is consistent with the observation that the dehydrochlorination of dichloroacetylchloride is a very fast reaction which occurs instantaneously even at -50°C. In our experimental conditions (addition of the acid chloride to a mixture of the Schiff base and triethylamine at room temperature) the elimination process was probably favoured over the acylation of the Schiff base by the acid chloride. However, when no triethylamine was present, dichloroacetylchloride and benzalaniline were found to yield quantitatively a 1:1 adduct, 8 ($\nu_{C=O}$ 1690-1700 cm^{-1} n.m.r. signals at 7.90 δ(s), 7.60-7.10 δ (m), 5.73 δ (s)) which formed the β-lactam 3d on melting (150°C) or refluxing in benzene solution. On addition of triethylamine at room temperature the yields were much lower (20-30 %) and a considerable amount of tars was obtained.



This result excludes 8 as the main precursor of 3d We thus believe that, under our experimental conditions, the evidence favours pathway a over pathway b although a small contribution of path b cannot be completely excluded (9) .

Further work in our laboratory is directed toward a more detailed study of these mechanistic pathways and the utilization of the reaction for the synthesis of biologically active β-lactams.

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