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ArchanaPathak*Dr.M.K.Pathak
Dr.Ashutosh Pathak *

SYNTHESIS OF CYCLOBUTAN-1-ONE DERIVATIVES BY THE REACTION OF KETENES WITH CHALCONES

Department Of Chemistry,
University Of Rajasthan, Jaipur *
Department Of Chemistry,
University Of Rajasthan,
Jaipur**Guru Kashi University,
Talwandi Sabo, Bathinda***

ABSTRACT

The reaction of haloketene and phenylketene with various chalcones and the chemistry of some of the reaction products have been investigated. The formation of cyclobutanone was taken as an indication that the reaction proceeds by an[2+2] cycloaddition in concerted mechanism. These all reactions create new opportunities to utilize the unique structures and high reactivity of ketenes for even greater progress in the future.

Mail:
shivanshupathak@yahoo.co.in

KEYWORDS: Ketenes, chalcone, cycloaddition, concerted mechanism

INTRODUCTION

Hermann Staudinger (23 March 1881-8 September 1965) was a German Chemist who demonstrated the existence of macromolecules. He is also known for his discovery of ketenes and of the Staudinger reaction. Ketenes would prove an synthetically important intermediate for the production of yet to be discovered antibiotics such as penicillin and amoxicillin.

Researchers in the U.S. and Korea have shown how an unusual functional group, which has been largely neglected in materials chemistry, can be incorporated into polymers to give the polymer both a reactive handle for attaching other molecules and a route to cross-linking adjacent polymer chains.

The ketene group $C=C=O$, is capable of rich and diverse chemistry, says Craig Hawker of University of California, Santa Barbara, who led the research with Bongilil Moon of Sogang University of Seoul, but has not been widely exploited in polymer chemistry. We speculate that polymer chemists have always viewed ketenes as simply too reactive to handle and too difficult to generate," says Hawker.

Ketenes are structurally interesting functional groups, and over the years have been the subject of intensive study that has been frequently reviewed. Cycloaddition reactions of ketenes have been the object of particularly great attention in recent years. Cycloadditions of ketenes with chalcones to form cyclobutan-1-one have been known for most of this century. And are probably the most complex and intriguing of the reactions classified by Woodward and Hoffmann as pericyclic⁵. The electronic interactions and geometry of the transition state have been the subject of much speculation.

It is somewhat paradoxical that ketenes are characterized by high electron density at the substituted carbon but as a result, there is an inverse correlation of computed ketene stabilization with substituent group electronegativities. Chloroketene is a highly reactive species in solution in an experimental tour de force by the reaction of dichloroacetyl chloride at low temperature. The high reactivity of haloketenes makes them very useful in synthesis as in the preparation of the enzyme inhibitor CP compound by [2+2] cycloaddition of chloroketene.

Mechanism and stereochemistry: Ketene cycloadditions proceed by a concerted [2+2] mechanism. Ketenes, unlike most alkenes, can align antarafacially with respect to other alkenes. Thus the suprafacial-antarafacial geometry required for concerted thermal [2+2] cycloaddition can be achieved in reaction of ketenes. This geometry has the interesting consequence that the bulkier substituent on the ketene will tend to end up on the more sterically hindered face of the cyclobutanone ring.

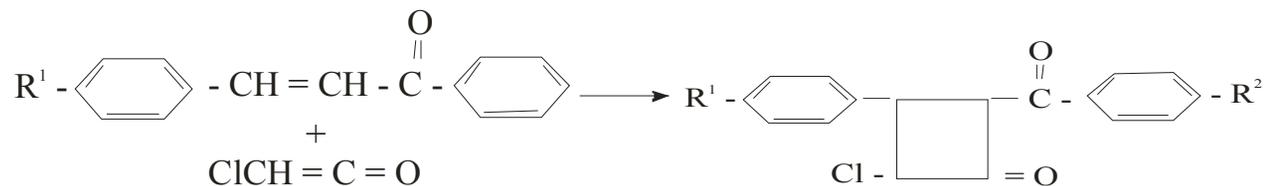
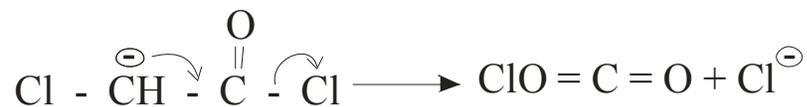
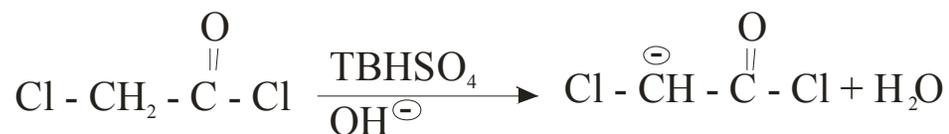
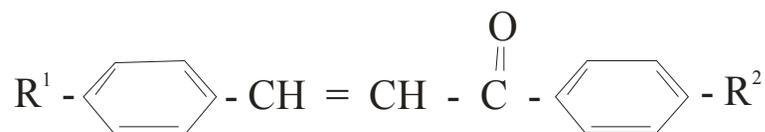
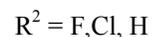
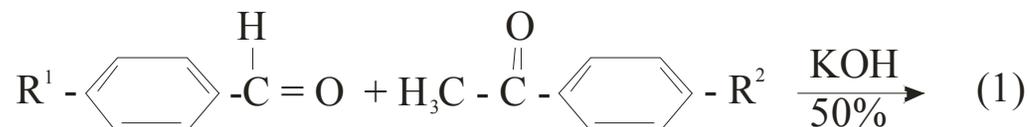
EXPERIMENTAL

Derivatives of cyclobutan-1-one are prepared by the reaction of chalcone with highly reactive ketenes in the presence of phase transfer catalyst such as TBHSO₄. Haloketenes were latecomers to the ketene family and were generated only as highly reactive species that were trapped as unobserved intermediates at low temperature.

Chalcones are prepared by the Claisen-Schmidt condensation of an acetophenone derivative with substituted benzaldehyde in the presence of KOH (50%). Place 3.3954 gm. [5 mmole] of TBHSO₄ in 20 ml of benzene and 1.35 ml of chloroacetyl chloride provided with a mechanical stirring. This reaction occurs at low temperature so immerse the reaction vessel in crushed ice. Highly reactive ketene generates in this reaction and after 15 min add chalcone. Stir vigorously until the

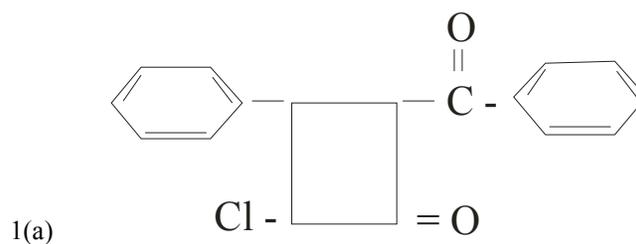
reaction are completed. Check the progress of reaction with the help of thin layer chromatography. The progress of the reaction can be estimated by disappearance of the characteristic yellow color of the ketene and by loss of the band at about 2100cm^{-2} in the infra red spectrum or by ^1H NMR spectroscopy. The success of the reaction is often determined by the relative rate of cycloaddition and dimerization of the ketene. After extraction with water, concentrate the solution and recrystallize by petroleum ether. Drying the product measure the M.P. of the compounds.

STRUCTURE

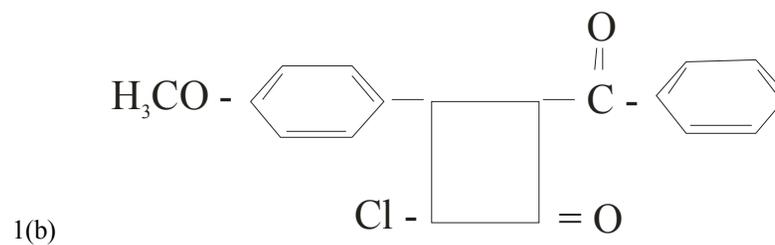


Compound	Molecular formula	Molecular weight	Yield (%)	Melting point(^o C)
1a	C ₁₇ H ₁₃ O ₂ Cl	284.5	58	230
1b	C ₁₈ H ₁₅ O ₃ Cl	314.5	55	210
1c	C ₁₇ H ₁₂ O ₂ Cl ₂	319	54	220
1d	C ₁₇ H ₁₁ O ₄ FCIN	347.5	60	222
1e	C ₁₈ H ₁₄ O ₂ Cl ₂	343	50	245

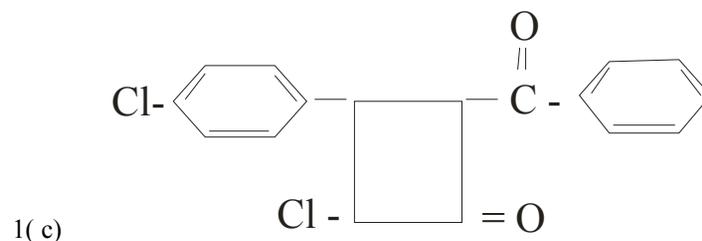
STRUCTURE



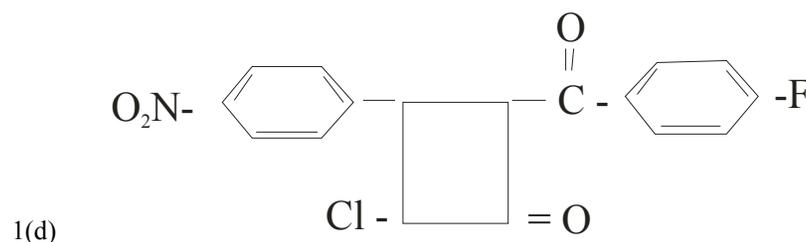
2 -Benzoyl 4-chloro 3- Phenyl cyclobutan-1-one



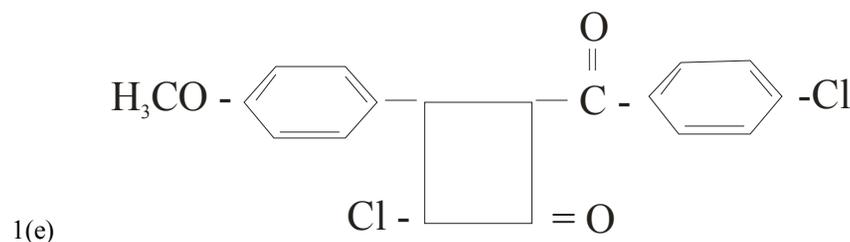
2- Benzoyl 4 -chloro 3-(4-Methoxy Phenyl)Cyclobutan 1 -one



2-Benzoyl 4-Chloro 3-(4-Chlorophenyl)cyclobutan-1-one



4-Chloro 2-[4-Fluorobenzoyl]3-[4-nitrophenyl] cyclobutan-1-one



2-[4-Chlorobenzoyl] 4-chloro 3-(4-Methoxy phenyl) cyclobutan-1-one

In the IR spectra of 2-Benzoyl 4-chloro-3-phenyl cyclobutane 1-one $\text{C}=\text{O}$ absorption appears as a sharp band at 1682cm^{-1} and 1705cm^{-1} which is due to $\text{C}_6\text{H}_5\text{C}=\text{O}$ and $\text{CH-C}=\text{O}$ group respectively. Characteristic absorption due to C-Cl appears at 750cm^{-1} . Other bands appear at 3022cm^{-1} (Ar-H), 2950cm^{-1} (C-H), 1620cm^{-1} (C=C). Appearance of signal at 3420cm^{-1} is due to the stretching vibration of O-H group which confirms the presence of Keto-enol tautomerism.

^1H NMR spectra Ar-H proton resonance signal appears as multiplet at 7.29-7.31 ppm (10H). A sharp double doublet due to $\text{CH-CH-C}=\text{O}$ group appears at 4.15-4.20 ppm (1H). The $\text{HC-CH}=\text{C}=\text{O}$ proton signal of cyclobutanone moiety appears as sharp singlet at 5.71 ppm. In compound 1a a singlet appears at $\delta 1.6$ ppm (3H) is due to the presence of CH_3O -group.

IR spectral data (cm⁻¹) of cyclobutan-1-one derivatives (1a-1e)

Compound	Ar-H	C-H	C=O	C=C	C-O-C	C-F	O-H	C-Cl
1.a	3022	2950	1682 1405	1620	1225		3420	750
1.b	3020	2950	1685	1632	1225		3380	700
1.c	3040	2960	1680	1630	1210	1250	3418	
1.d	3030	2945	1680	1650	1220		3450	705
1.e	3025	2950	1686	1450 1650	1218		3460	700

TABLE 3 ¹H NMR Spectral data (δppm) of cyclobutan 1 –one derivatives (1a -1e)

Compound	Ar-H	CH-CH=C=O	CH-CH-Cl	Cl-CH-C=O	-OH	CH ₃ -O-
1.a	7.29-7.31 m,10H	5.71 d, j = 2.27Hz 1H	4.15-4.20 (m,1H)	2.07 (d,j=3.47, 1H)	4.50 (s,1H)	
1b	7.20-7.30 (m,9H)	5.30 (d, J=2.36 Hz 1H)	4.12-4.16 (m,1H)	2.24 (d J = 3.66 1 H)	4.4 (s,1H)	1.6 (s,3H)
1.c	7.23-7.36 (m,9H)	5.34 (d,J=2.36 1H)	4.12-4.14 (m,1H)	2.17 (d, J=3.6Hz 1H)	4.25 (s,1H)	
1.d	7.24-7.36 (m,8H)	5.33 (d,J=2.36 Hz 1H)	4.10-4.15 (m,1H)	2.22 (d, J= 3.65 Hz 1H)	4.08 (s,1H)	
1.e	7.21-7.46 (m,14H)	5.21 (d,J=2.37 1H)	4.08-4.12 (m,1H)	2.25 (d,J=3.66 Hz, 1H)	4.10 (s,1H)	

MICROBIAL ACTIVITY

Organic compounds containing four member ring present a unique group of metabolites, including natural products and drugs. The cyclobutanone unit is found as a basic structure element in a wide range of naturally occurring compounds in bacteria, fungi, plants and marine invertebrates. Many biological activities are shown and may serve as potential drug leads or provide new idea for the study of enzyme mechanism and organic synthesis. Some cyclobutanone compounds such amino-acids, peptides, and nucleosides show protective properties against ultraviolet radiation. In the skin, many molecules may absorb UV radiation upon exposure.

Bacterial resistance to antibiotics is an emerging epidemic throughout the world and there is a need desperate need for new antibiotics and new strategies to maintain the effectiveness of current agents. Cyclobutanone analogues of β -Lactam antibiotics were explored in the early 1980 as potential inhibitors of β -Lactamases and D-Ala-D-Ala transpeptidases. Cyclobutanones have the potential to exhibit broad-spectrum inhibition of both serine and metallo- β -Lactamases through the formation of enzyme bound hemiketals or hydrates.

FOOD TECHNOLOGY

Ionizing radiation e.g. γ -irradiation, for the preservation of foods is not generally accepted and allowed. The development of tests for the detection of irradiated foods is of importance in this matter. Together with a good management at the irradiation facility, such tests would facilitate international trade and increase consumer confidence in the existing control procedures. The detection of 2-substituted cyclobutanones as markers for γ -irradiated foods proved to be very successful for chicken, peanuts, papaya, liquid whole egg pork, lamb, beef and fish.

CONCLUSION

From the above review, it can be said that cyclobutanone and their derivatives display a wide range of pharmacological activities, such as antibacterial, anti-inflammatory and broad spectrum inhibition of both serine and metallo- β -Lactamases with good protective properties against ultraviolet radiation. Because of this, chalcones and their derivatives have attracted increasing attention of the scientists for the search of new potent pharmacological activity in it.

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