Synthesis and Characterization of Some β- Lactams Derivatives from 5-Phenyl Valeric Acide

تخليق وتشخيص لبعض مركبات البيتالاكتام الجديدة والمشتقة من حامض الفاليرك

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Abstract

A series of 3-(3-phenylpropyl)azetidine-2-one 3(a-d), have been synthesized via Schiff bases 2(a-d) in the presence of triethylamine with phosphorusoxychloride using dry methylene chloride under nitrogen atmosphere at 0 ˚C. The active acid chloride reacts with triethylamine to generate corresponding ketene in situ which further react with Schiff's base to furnish the corresponding 3-(3-phenylpropyl) azetidine-2-one 3(a-d) in moderate yields.. The mass spectroscopy confirms the molecular weight of the prepared compound. Furthermore, the two dimensional NM HMQC ^{1}H-^{13}C, COSY ^{1}H–^{1}H was used to confirm the proposed structure.

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الخلاصة

تضمنت الدراسة تخليق وتشخيص بعض مركبات 3- (3-بروبيل فنيل) ازيتيدين-2-ون التي تم تحضيرها من تفاعل حامض الفاليرك مع بعض قواعد شف بوجود ثلاثي اثيل امين واوكسي كلوريد الفسفور في كلوريد الاثيلين الجاف عند درجه الصفر المئوي. حيث ينتج كيتين والذي يتفاعل مع قواعد شف ليعطي الناتج ازيتيدين-2-ون.شخصت المركبات باستخدام اطياف تحت الحمراء وطيف الكتلة ومطيافيه الرنين النووي المغناطيسي البروتوني وكاربون 13 واقتران طيف الرنين البروتوني والبروتوني وكاربون 13.

Introduction

The β-lactams are most extensively studied classes of compound due to their biological activity[1]. The β-lactams class of drugs revolutionized the treatment in medicine. These compounds are four-membered cyclic amides. Figure 1 represents the essential structural feature of penicillin and cephalosporins[2].

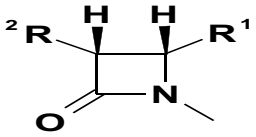


Figure 1

Burnett and coworkers have described the synthesis of a very potent class of cholesterol absorption inhibitors (CAI) typified by the original lead compound in this series: the compound I showed in Fig. 2 (SCH 48461). This 2-azetidinone has resulted as an effective inhibitor of cholesterol absorption in a cholesterol-fed hamster model[3] .Subsequently, the same molecule has been shown to reduce serum cholesterol in human clinical trials[4]. Although this class of compounds has been initially designed as acyl coenzyme A cholesterol transferases (ACAT) inhibitors, early structure-activity studies demonstrated a striking divergence of in vitro ACAT inhibition and in vivo activity in the cholesterol-fed hamster. A detailed examination of this molecule indicated that the hypocholesterolemic.

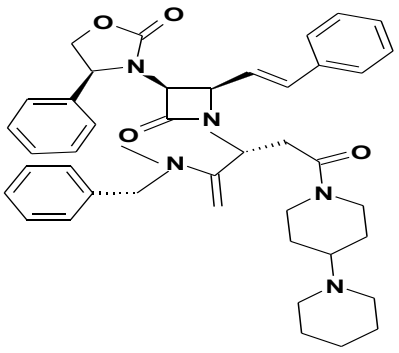


FIGURE 2

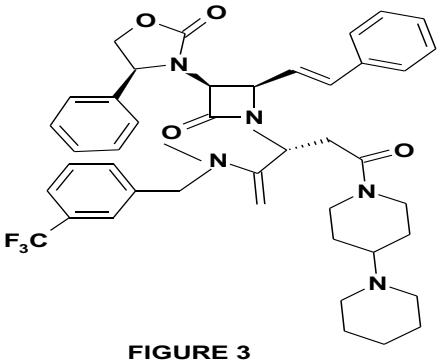
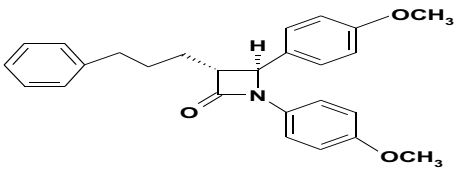
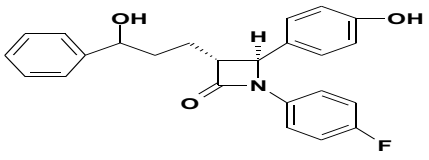


FIGURE 3





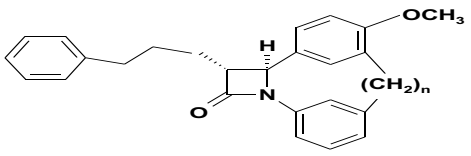
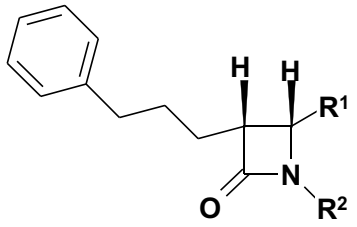


Figure-4-

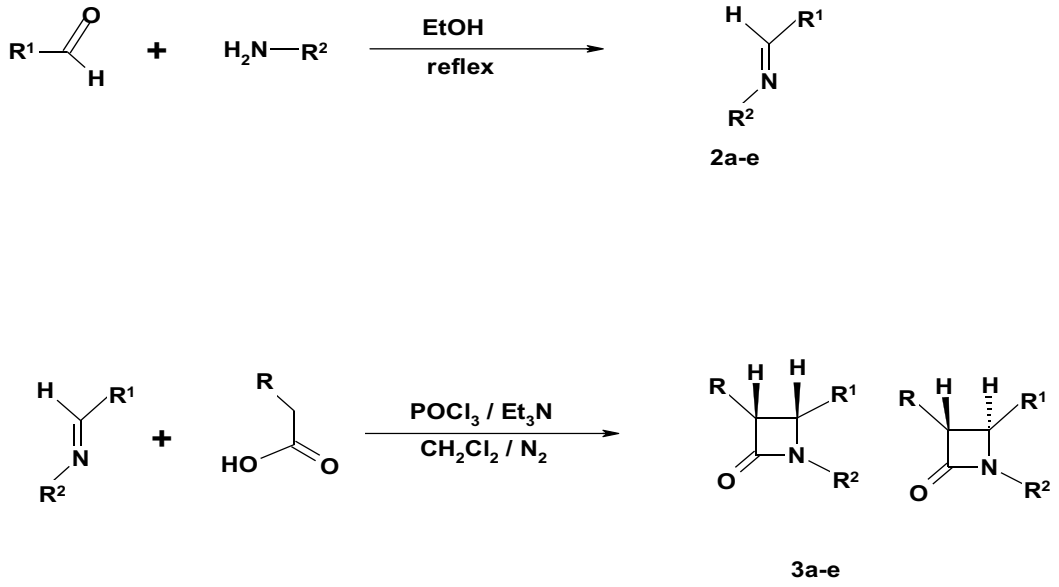
Result and Discussion

Taking a lead from recent earlier studies[4, 5,6,7] we considered to utilize ketene-imine cyclization in the presence of triethylamine for the synthesis of 3-(3-phenylpropyl)azetidine-2-ones substituted of β- lactam of type A .



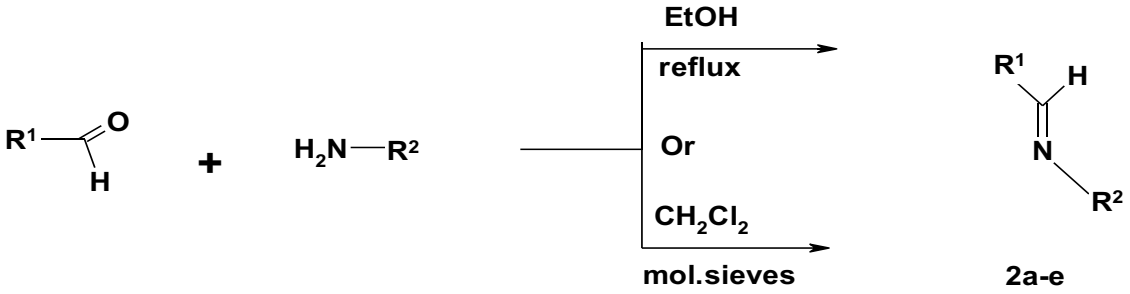
A

In view of the associated biological activity and utility in organic synthesis, the synthesis of 3-(3-phenylprppyl)azetidine-2-one3(a-d) was performed. The key step involved the treatment of the imine 2(a-d) with 5-phenylvalericacid by using triethylamine in the presence of phosphorusoxychloride in dry methylenechloride under nitrogen to afford azetidine-2-one 3(a-d) , as shown in scheme 1.



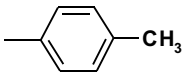
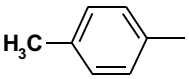
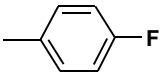
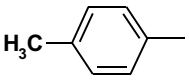
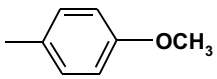
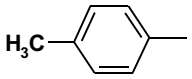
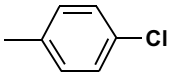
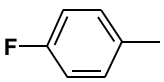
Scheme 1

The target β-lactam 3(a-d) required for this study was prepared by treatment 5-phenylvalericacid with the appropriate Schiff's bases 2(a-d) by using triethylamine as a base in dimethylenechloride at 0C sieves (4Aº) or in hot ethanol .The structures of the imines were confirmed on the basis of their spectra data, IR and NMRspectra.Various Schiff's bases 2(a-d) were prepared from the appropriate aldehydes and amines in methylenechloride in the presence of molecularsieves.



Scheme 2

Table 1:The Schiff's bases 2(a-d).

Schiff's bases	R^1	R^2
2a		
2b		
2c		
2d		

The active acidchloride reacted with triethylamine to generate the correspon ding ketene in situ which further reacted with Schiff's base to furnish the corresp onding β-lactam in moderate yields ,as shown in Scheme 3.

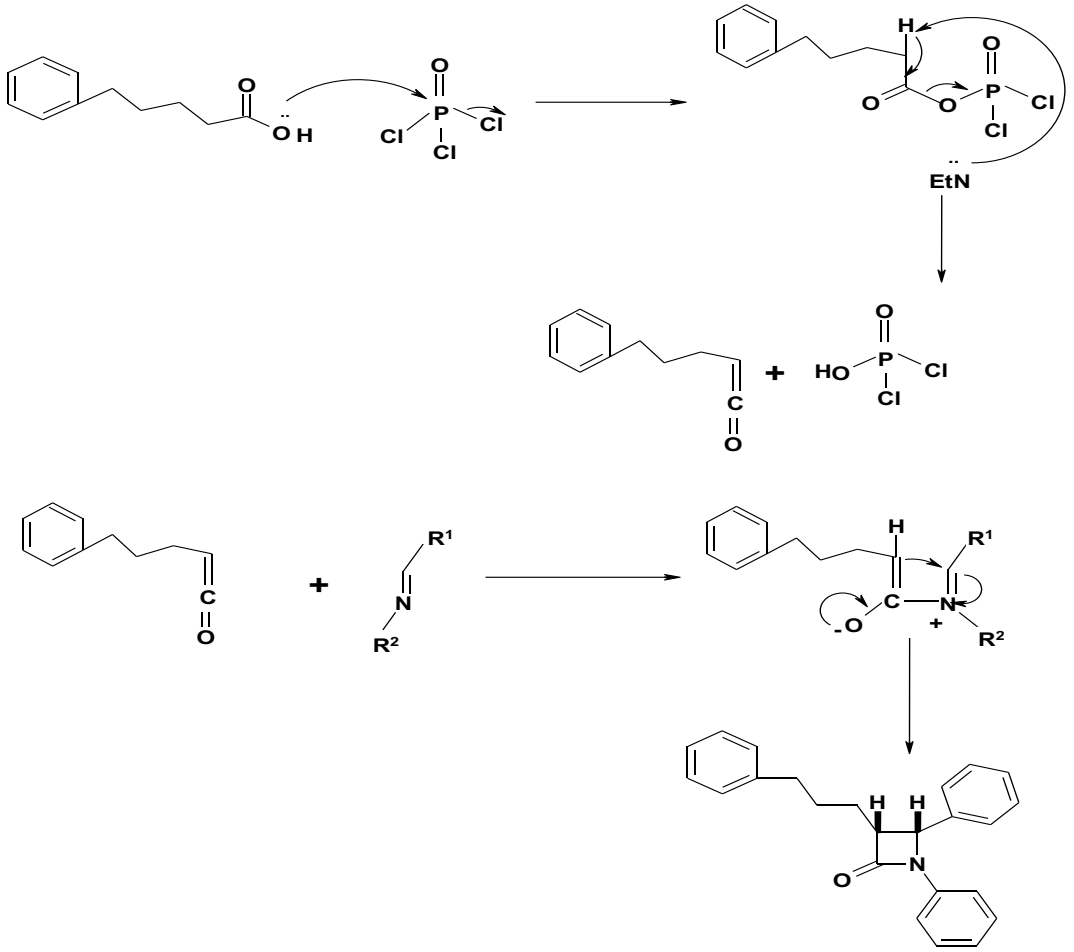
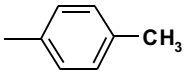
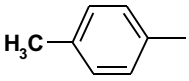
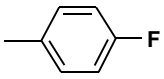
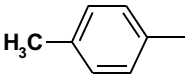
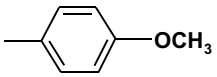
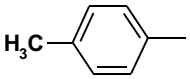
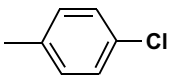
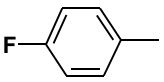


Table 2: 3-(3-phenylpropyl) azetidine -2-ones 3(a-d).

Comp	R^1	R^2
3a		
3b		
3c		
3d		

The **IR** spectra of the 3-(3-phenylpropyl)azetidine-2-one **3(a-d)** as KBr disc and their representative spectra, are shown in Table 3-3 and Figures (3-1) -(3-10).The spectra of the 3-(3-phenylpropyl)azetidine-2-ones **3(a-d)** are characterized by the five bands corresponding to the stretching vibrations of the aromatic C-H, aliphatic C-H, carbonyl group,alkene and substituted ring which occurs within the ranges 3186-3025,2931- 2858,1653-1651,1600-1523 and 835-815 cm^{-1}, respectively[8].The substitution of the phenyl ring by electron-donating groups such as methoxy group ,decreased the absorption frequencies, whereas the substitution by an electron-withdrawing chloro group increased the absorption frequency at 1651Cm^{-1} and 1653cm^{-1}, respectively.[9]

The ^{1}H-NMR of β-lactam showed two regions,an aliphatic region including two groups of signals at the region δ 1.696-1.819 ppm and δ 2.322-2.690 ppm, corresponding to methylene , C_3-H, and C_4-H protons.In the ^{1}H-NMR spectra of the aromatic region ,the situation is different scine the close similarity of the electronic environment of the aromatic protons makes an arrow range of the chemical shift and in many cases the spectra lines are superimposed[10]upon each other. In spite of formula similarity, we can notice two doublet at the range of δ6.995-7.030 ppm and 7.115-7.473 ppm corresponding to 13H of β-lactam derivatives 3(a-d)which are included in Table(4)with their representative spectra.

The 2D NMR COSY^{1}H-^{1}H studies led to the assignment of signals to protons and protons in the azetidine-2-ones 3d.The application of cosy using ^{1}H-^{1}H NMR spectra in characterization of such compounds is discussed successfully by taking representative example of 3d, in Figures (3-24) and (3-25). The Cosy ^{1}H-^{1}H NMR of compound 3e showed aliphatic protons 1.704, 1.789, 2.354, 2.369, 2.383, 2.661,2.675 and2.690 ppm in correlation with aliphatic proton at 1.704,1.789,2.354, 2.369,2.383,2.6612.675 and 2.690 ppm, respectively .The Cosy ^{1}H-^{1}H-NMR of compound 3e showed an aromatic proton at 6.99,7.01,7.03,7.186,7.200,7.276, 7.2947.310, 7.445 and 7.455 ppm in correlation with aromatic proton at 6.99, 7.01, 7.03, 7.186, 7.20, 7.276 7.294, 7.310 7.445 and 7.455, respectively.

2D NMR HMQC ^{1}H-^{13}C spectra .

The 2D NMR HMQC ^{1}H-^{1}H spectra of the 3b showed the correlation of the methyl proton in compound 3c signal at δ2.322 ppm with carbon signal at δ21.32ppm, which led to the assignment of this signal to methyl group carbon.

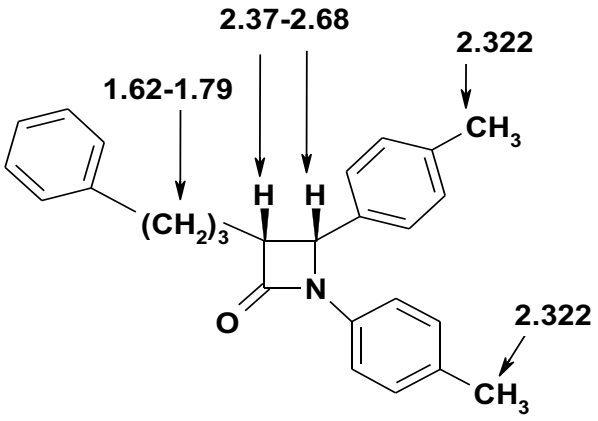
The HMQC spectra showed the correlation of proton signals at 2.346-2.391 ppm and 2.665-2.684 ppm with carbon signals at δ35.91 and 37.57 ppm.

The aromatic protons from δ7.115,7.310,7.186, 7.215, 7.276, 7.309, 7.383 and 7.399 ppm correlation with carbon aromatic signals at 119.80,125.71, 128.87, 129.23, 135.10,137.30 at 142.01 ppm Figures (3-11),(3-12),(3-13) and(3-14).

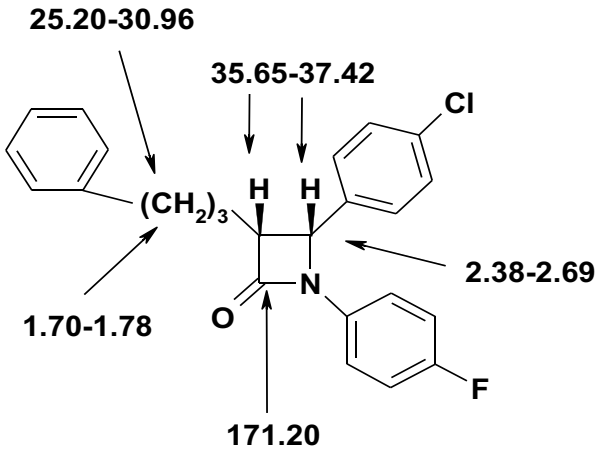
The ^{1}H-^{13}C spectra of the 3d showed the correlation of protons signals at 2.354-2.393 ppm and 2.661-2.690 ppm with carbon signals at 35.65 ppm and 37.42 ppm, respectively.

The aromatic protons from signals 6.995,7.013,7.030,7.186,7.200, 7.276,7.294,7.310,7.445 and 7.455 ppm were in correlation with aromatic carbons

115.48,115.66,121.72,125.84,128.37,133.84 and 142.03ppm respectively, as shown in Figures (3-21),(3-22) and (3-23).



compound 3a



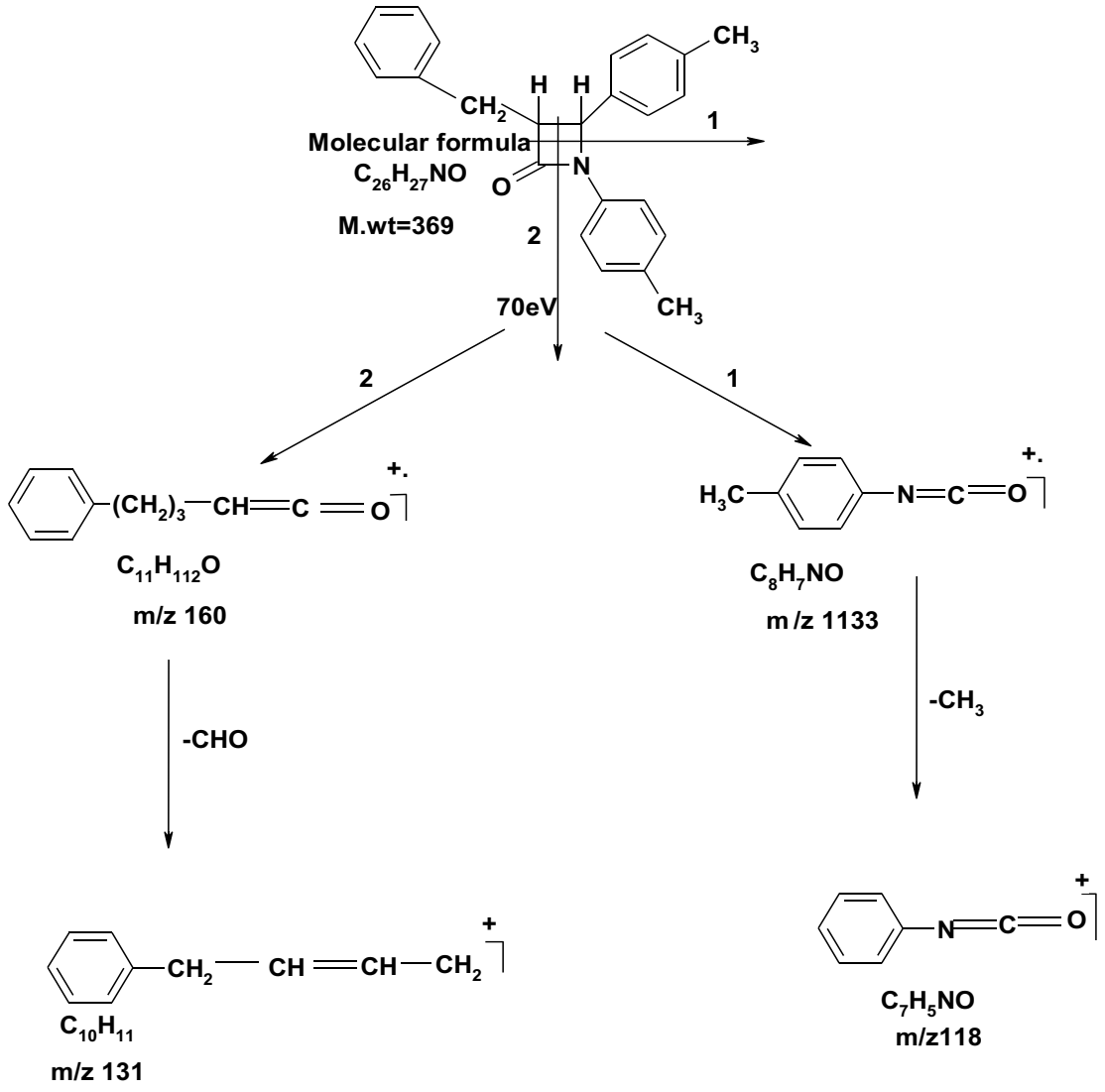
compound 3e

The ^{13}C NMR spectra of the 3c,3d and 3e of the azetidine -2-ones showed a similar pattern .The resonance as between δ171.01-171.21 ppm were assigned to the carbonyl[11]groups,methylene group within the range δ24.1-33.71ppm and methyl group within range δ20.84-21.32ppm.The chemical shift values of aromatic carbon atoms within the range 115.48-142.03ppm are shown in Figures (3-10),(3-17) and (3-20).

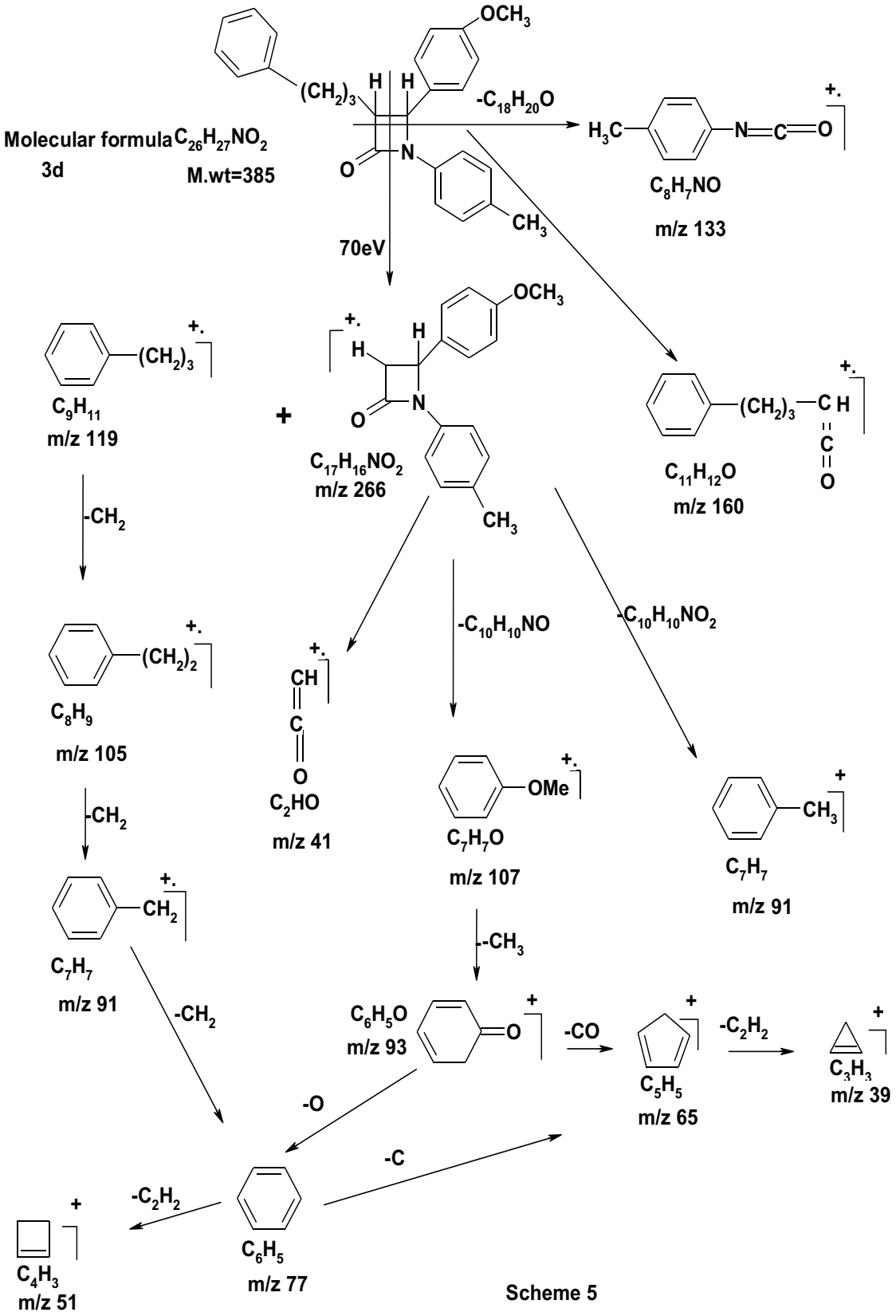
The DEPT ^{13}C NMR in 135, as shown in Figures(3-26),showed the methylene group in 3-(3-phenylpropyl)azetidine-2-one 3e at 25.16(-) ,30.94(-) and 35.63(-) ppm,while the aromatic carbons apparent at 115.48(+), 115.66(+), 121.56(+), 121.65(+), 125.28(+), 128.34(+) and 128.38(+) ppm. The mass spectral data of the prepared derivatives are gathered in the Figures (3-28), (3-29), (3-30), (3-31) and (3-32).

Mass spectra of products don't show a molecular ion M^+ peak, because the direct synthesis of 3-alkyl-β- lactams from monoalkyl-ketene , generated from their corresponding acidchloride, is often limited in scope. That fact is probably due to the inherent instability of aldoketene[12,13].

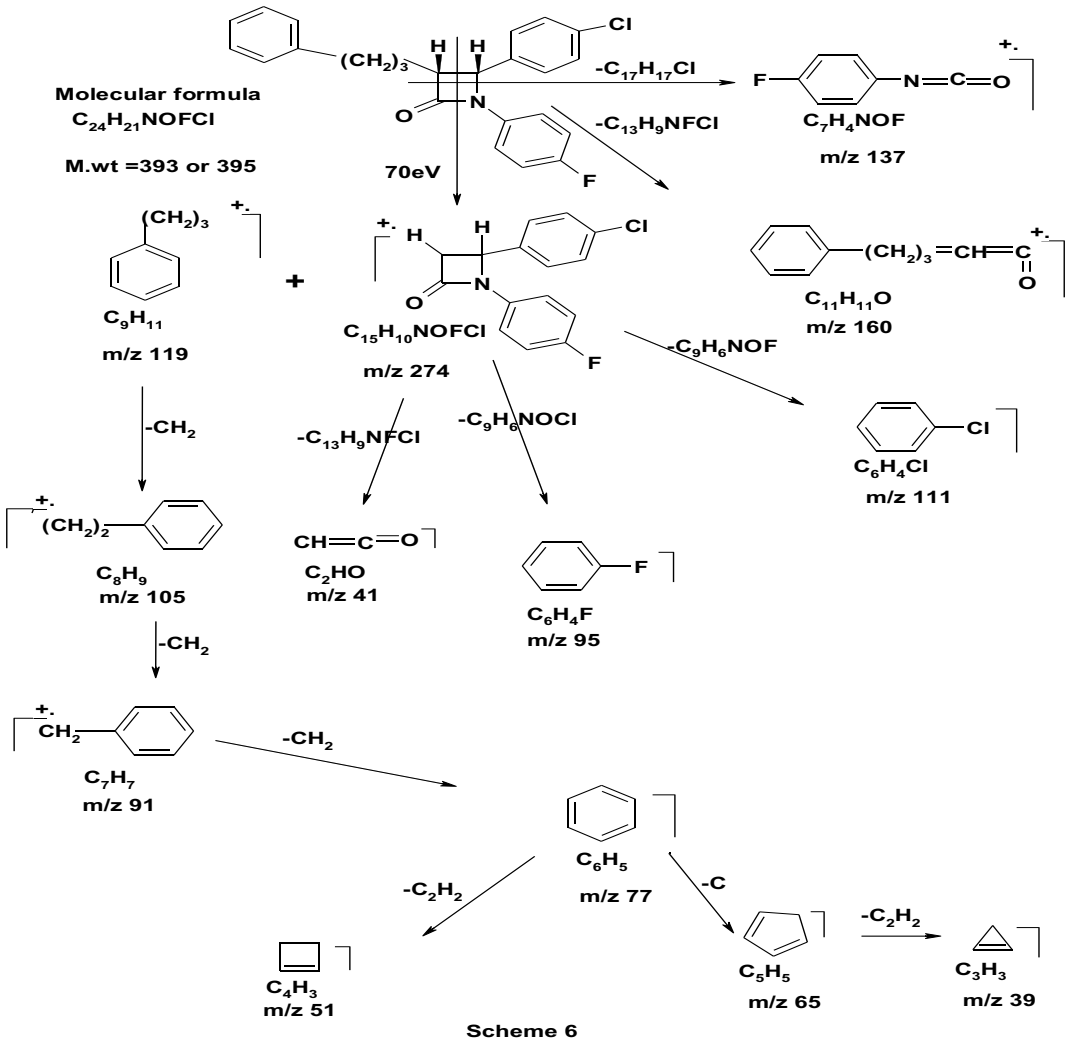
The mass spectra of the products are similar. The fragmentation of the azetidine-2-one leads to ketene, isocyantes and imine. The fragmentation of 3(a-d) showed the peaks at 231m/z, 160 m/z ,133m/z 107m/z ,91m/z , 77m/z, 65m/z, 51m/z, 39m/z are attributed to the fragments ,imine $[C_{14}H_{12}NCl]^+$, ketene $[C_{11}H_{12}O]^+$, isocyanate $[C_8H_7NO]^+$,$[C_8H_9]^+$, $[C_7H_5]^+$, $[C_5H_5]^+$, $[C_4H_3]^+$, and $[C_3H_3]^+$ respectively, the fragmentation mechanism of compounds 3(a-e) is shown below [14,15] in Schemes 4,5and6.



Scheme 4


Molecular formula $C_{26}H_{27}NO_2$
3d
M.wt=385
$-C_{18}H_{20}O$
$H_3C-N=C=O$
C_8H_7NO
m/z 133
70eV
C_9H_{11}
m/z 119
$C_{17}H_{16}NO_2$
m/z 266
$C_{11}H_{12}O$
m/z 160
$-CH_2$
C_8H_9
m/z 105
$-C_{10}H_{10}NO$
$-C_{10}H_{10}NO_2$
C_2HO
m/z 41
C_7H_7O
m/z 107
C_7H_7
m/z 91
$-CH_3$
C_6H_5O
m/z 93
-CO
C_5H_5
m/z 65
$-C_2H_2$
C_3H_3
m/z 39
-O
-C
$-C_2H_2$
C_6H_5
m/z 77
C_4H_3
m/z 51

Scheme 5



Scheme 6

Preparation of Schiff bases 2(a-d)[16,17]

General procedure

A mixture of an appropriate aromatic amine (0.01 mole) and an aromatic aldehyde (0.01 mole) in 20 ml of absolute ethanol and one drop of glacial acetic acid were heated in water bath at (70-80C^0) for 30min.The progress of the reaction was checked by TLC. After completion, the solvent was evaporated then recryastalized from a suitable solvent, as shown Table 2-2.The following are the Schiff bases and the reactants which are used in their preparations by the above general procedure.

4.1: N-(4-methylphenyl)-4-methyl benzyldine 2a

The compound was prepared by treatment of 4- methyl aniline (0.01mole,1.07g) and 4-methylbenzaldehyde (0.01mole,1.192g).

4.2: N-(4-methylphenyl)-4-fluorobenzylidine 2b

The compound was prepared by the treatment of 4-methyl aniline (0.01mole,1.07g) and 4-fluorobenzaldehyde (0.01mole,1.24g).

4.3:N-(4-methylphenyl)-4-methoxybenzyldine2c.

It was prepared by the reaction 4-methylaniline (0.01mole,1.07g) and 4-methoxybenzaldehyde (0.01mole,1.36g).

4.4.N-(4-methylphenyl)-4-fluorobenzylidine2d.

The compound was prepared by the treatment of 4-fluoroaniline (0.01mole,1.11g) and 4-chlorobenzaldehyde (0.01mole,1.405g)

Table (3): physical data of Schiff's bases2(a-d)

Schiff's bases	m.p°c	Yield%	Color	Solvent of recrystalization
2a	98-100	80	white	Ethanol
2c	63-65	78	Yellowish	Ethanol
2d	97-99	87	Yellow	Ethanol
2e	76-78	75	Yellowish	Methanol

5-Preparation of 3-(3-Phenylpropyl)azetidine-2-one 3(a-d)[18,19,20] :

5.1:1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(4-methylphenyl)azetidine-2-one 3a.

To a mixture of 5-phenylvaleric acid (0.85g, 1.5 mmole), N-(4-methylphenyl)-4-methylbenzylidine2a(1.0g,1mmole)and triethylamine (0.85g,3mmole,1.98mL) in dry dichloromethane 40mL at 0ºC under N_2 atmosphere,a solution of $POCl_3$ (0.733g, 1.5mmole,0.65mL) in dry dichloromethane 20mL was added as drop wise. The mixture was stirred over night at room temperature .There after, the contents were washed successively with 1N HCl 20mL ,5%$NaHCO_3$ 20mL and brine 20mL.The organic layer was separated and dried over anhydrous Sodiumsulphate Na_2SO_4.The solvent was removed under reduced pressure and the crude product was column chrompotographed over silica gel using ethylacetate-hexane 2:8 as eleuent and solvent evaporation furnished pure –β-lactam 3a. Yield= 85. %, m.p °C (97-99); FT-IR (KBr

disk): 1651 cm-1; 1H (CDCl3) ppm: 1.82 (m, 2H, CH2), 2.37 (m, 2H, CH2), 2.68 (m, 2H, CH2), 7.11-7.36 (m, 13H, aromatic), 13C NMR (CDCl3) ppm: 21.32,26.10,31.42,35.91,37.91,119.18,125.71,128.87,129.23,135.10,137.30,142.01,171.01

5.3:1-(4-Methylphenyl)-3-(3-phenylpropyl)-4-(fluorophenyl)azetidine-2-one 3b

To a mixture of 5-phenylvaleric acid (0.775g,1.5mmole) , N-(4-methylphenyl)-4-fluorobenzylidine 2b(1.0g,1mmole) and triethyl-aniline(0.44g,3mmole,1.95mL)in 40 mL of dry dichloromethane at 0ºC under N_2 atmosphere, a solution of $POCl_3$ (0.719g,1.5mmole,0.64mL) in dry dichloromethane 20mL at was added drop wise. The reaction mixture after completion of reaction, was worked up as usual. The crude product was columned over silica gel using ethylacetate-hexane 2:8 as eluent and solvent evaporation furnished pure- β-lactam 3C.

Yield = 80%, m.p. °C (80-81); FT-IR (KBr disk) : 1651 cm-1; 1H-NMR (CDCl3) ppm: 1.81 (m, 2H, CH2),2.37 (m, 2H, CH2), 2.68 (m, 2H, CH2), 7.11-7.36(m, 13H, aromatic); 13C-NMR (CDCl3) ppm: 21.32,26.10,31.42,35.91,37.91,119.18,125.71,128.87,129.23,135.10,137.30,142.01,171.01

5.4:1-(4-Methylphenyl)-3-(3-phenylpropyl)-4(4-methoxyphenyl)azetidine-2-one 3c

To a mixture of 5-phenylvalericacid (0.791g,1.5mmole), and N-(4-methyl phenyl)-4-methoxybenzyllidine2d (1.0g,1mmole) and triethyl-amine (0.448g, 3mmole, 1.84mL) in dry methylenechloride 40mL at 0ºC under N_2 atmosphere, a solution of $POCl_3$ (0.68g, 1.5mmole, 0.61mL) in dry methylenechloride 20mL was added drop wise .The reaction mixture after completion of reaction was worked up as usual. The crude product was column over silica gel using ethylacetate-hexane 2:8 as eluent and solvent evaporation furnished pure-β-lacatam 3d. Yield =65%, m.p. °C (99-101); FT-IR (KBr disk) : 1651 cm-1; 1H-NMR (CDCl3) ppm: 1.81 (m, 2H,

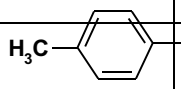
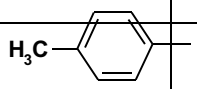
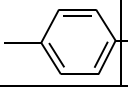
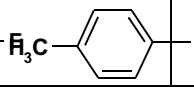
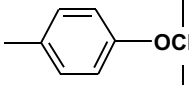
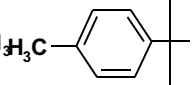
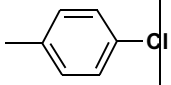
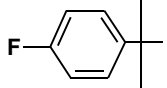
CH2), 2.4 (m, 2H, CH2), 2.6 (m, 2H, , CH2), 7.11-7.29 (m, 13H, aromatic); 13C-NMR (CDCl3) ppm: 20.84,25.27,31.01,35.59,37.57,119.89,125.80,128.34,128.40,129.54,133.82,135.32,142.13,171.0.

5.5:1-(4-Fluorophenyl)-3-(3-phenylprophyl)-4-(4-chlorophenyl) azetidine-2-one 3d

To a mixture of 5-phenylvalericacid (0.762 g,1.5mmole), N-(4-florophenyl)-4-chlorobenzylidine2e (1.0g,1mmole) and triethylamine (0.435g,3mmole,1.77mL) in dry methylenechloride 40mL at 0^0C under N_2 atm,a solution of $POCl_3$ (0.656g ,1.5 mmole,0.58mL) in dry methylenechloride 20mL was added dropwise.The reaction mixture after completion of reaction, was worked up as usual. The crude product was column over silica gel using ethyl acetate-hexane 2:8 eluent and solvent evaporation furnished pure –β-lactam 3e. Yield =72%, m.p. °C (124-126); FT-IR (KBr disk) : 1653 cm-1; 1H-NMR (CDCl3) ppm: 1.806 (m, 2H, CH2), 2.39 (m, 2H, CH2), 2.69

(m, 2H, CH2), 6.99-7.47 (m, 13H, aromatic); 13C-NMR (CDCl3) ppm: 24.34,25.20,30.96,35.69,37.42,115.48,115.66,121.72,125.84,128.37,133.84,142.03,171.20.

Table (4).:Physical properties of 3-(3-phenylpropyl)azetidine-2-ones3(a-d).

Comp	R_1	R_2	Yield %	m.p ºC	Colour
3a			85	97-99	White
3b			80	80-81	White
3c			65	99-101	White
3d			72	85-87	White

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