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Experimental and theoretical rearrangement of N-acyl-2,2-dimethylaziridines in acidic medium

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Abstract. The acid isomerization of N-acyl-2,2-dimethylaziridines **1** in concentrated sulfuric acid at room temperature leads to oxazolines **2** but the neutral hydrolysis of **1** in pure water at room temperature leads to amidoalcohols **3**. However, the use of aqueous solutions of H_2SO_4 at different concentrations at room temperature leads to a mixture of oxazolines **2**, amidoalcohols **3** and allylamides **4** with yields depending on the acidity of the medium and the nature of the acyl group. A mechanism has been suggested to explain the formation of these three products. DFT calculations employing the Gaussian 09 program with DFT/B3LYP methods and 6-311++G(2d,2p) basis set were carried out which gave the most stable geometry as well as their atomic charge distributions of compounds **1-4**.

Keywords. N-acylaziridine; hydrolysis; isomerization; DFT calculations.

1. Introduction

It is well-known that the aziridines derivatives exhibit biological and pharmacological activities.[1–4] Aziridines can be also used to functionalize polymers[5–8] by ring opening of their heterocycles. The reactions of N-acylaziridines with various thiols give the corresponding amido sulfide products by an attack of the nucleophile on the less substituted carbon of the heterocycle are reported in literature.[9] Moreover, N-acetylaziridine is converted into the L-allothreonine, by ring opening with Ac_2O-Pyr on the C_3 carbon side of aziridine.[10] On the other hand, the synthesis of methylene aminodipeptides was obtained by competitive nucleophilic attack of primary amines on the C_2 and C_3 carbons of 2(t-butoxycarbonyl methyl) aziridine derivatives.[11]

In our previous investigations, we have already demonstrated that the N-aroylaziridines react with sodium iodide in acetone to give a mixture of oxazolines and allylamides. Such a reaction resulted by the breaking of the C-N bonds.[12] However, the ethanolysis in the presence of sodium perchlorate[13] and neutral hydrolysis[14] of various N-activated aziridines yielded the corresponding products by selective nucleophilic attack of ethanol and water on the most substituted carbon.

In addition, we have studied the isomerization of N-cinnamoyl-2,2-dimethylaziridine by concentrated sulfuric acid which led to the corresponding oxazoline by regiospecific ring opening on the $C(Me)_2$ carbon side of aziridine.[15] However, Eastwood[16] reported that the treatment of isopropyl N-benzoyl-2-carboxylate with the same Bronsted acid gives a mixture of two oxazolines and two amidoalcohols resulting from the competitive isomerization and hydrolysis reactions.

More recently, we investigated the reaction of hydrated acid-activated clays with N-acyl-2,2-dimethylaziridines **1**. A mixture of oxazolines, methallylamides and amidoalcohols was formed and the yields closely depended upon the aziridines **1**.[17,18]

In order to improve the selectivity of the reaction and to increase in the overall yield, we have now studied the acid hydrolysis reaction of N-acyl-2,2-dimethylaziridines.

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2. Experimental

2.1 *Materials, methods and instruments*

The infrared spectra were recorded in CH_2Cl_2 on a Bruker spectrometer IFS66V/S -IR 420 (between 400 and 4000 cm^{-1}). The ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AC spectrometer (300 MHz ^1H frequency). The ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC spectrometer (75 MHz ^{13}C frequency). Chemical shifts are reported in ppm from internal TMS. Silica gel (70–230 mesh, Merck) was used for the separation by column chromatography.

2.2 *Synthesis*

2.2a *Synthesis of N-acylaziridines*: N-acyl-2,2-dimethylaziridines **1a-e** were prepared from 2,2-dimethylaziridine and various acyl chorides with an excess of triethylamine in dry benzene according to known procedures.[19]

2.2b *Typical procedure of the rearrangement of N-acylaziridines **1***:

2.2b1 *Reaction of conc. H_2SO_4 with N-acylaziridines **1***: A cold 30 mL of conc. sulfuric acid was added to 2 mmol of aziridine **1** at a low temperature and then stirred at room temperature for 2 h 30 min. The reaction was quenched with 10% NaOH and the aqueous mixture was extracted with ether (3 × 100 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated to give oxazoline **2**.

2.2b2 *Reaction of ultrapure water with N-acylaziridines **1***: A mixture of 2 mmol of aziridine **1**, 2 mL of ether and 10 mL of ultrapure water was stirred at room temperature for 96 h. The mixture was extracted with ether (3 × 100 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated to give amidoalcohol **3**.

2.2b3 *Reaction of N-acylaziridines **1** with a mixture of water and sulfuric acid in different concentration*: A cold solution of 9% or 48% H_2SO_4 by wt. in water was added to a mixture of 2 mmol of aziridine **1** in 2 mL of ether at a low temperature and then stirred at room temperature for 96 h. The crude reaction was quenched with 10% NaOH to neutral pH, and the aqueous mixture was extracted with ether (3 × 100 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated to give a mixture of compounds **2-4**. The products were purified by column chromatography (silica gel, Petroleum ether / Ethyl ether: 20/80 for the compound **2**, Ethyl ether/Ethyl acétate: 90/10 for the compound **3**, Petroleum ether /Ethyl ether: 50/40 for the compound **4**).

2.3 *Analytical data*

*N-propanoyl-2,2-dimethylaziridine **(1a)***. IR (CH_2Cl_2, cm^{-1}): ν (C=O) 1678. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15 (3H, q, J = 6 Hz, CH_3), 1.35 (6H, s, $2CH_3$), 2.12 (2H, s, CH_2N), 2.35 (2H, t, J = 6 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 9.32 (CH_3), 23.06 (CH_3), 30.92 (CH_2), 36.82 (CH_2N), 40.65 (Cq), 185.32 (C=O).

*5,5-dimethyl-2-propyloxazoline **(2a)***. IR: (CH_2Cl_2, cm^{-1}): ν (C=N) 1662. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.18 (3H, t, J = 6 Hz, CH_3), 1.40 (6H, s, $2CH_3$), 2.28 (2H, q, J = 6 Hz, CH_2), 3.55 (2H, s, CH_2N). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 10.02 (CH_3), 21.91 (CH_2), 27.33 ($2CH_3$), 66.43 (CH_2N), 83.41 (Cq), 168.34 (C=N).

*N-(2-hydroxy-2-methylpropyl)propylamide **(3a)***. IR (CH_2Cl_2, cm^{-1}): ν (C=O) 1657, (NH) 3443, (OH) 3585. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12 (2H, t, J = 6 Hz, CH_2), 1.28 (6 H, s, $2CH_3$), 2.28 (2H, q, J = 6 Hz, CH_2), 2.56 (1H, s, OH), 3.27 (2H, s, CH_2N), 6.22 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 10.06 (CH_3), 27.21 ($2CH_3$), 29.59 (CH_2), 50.36 (CH_2N), 70.77 (Cq), 175.13 (C=O).

*N-(2-methylprop-2-enyl)-propylamide **(4a)***. IR (CH_2Cl_2, cm^{-1}): ν (C=C) 1648, (C=O) 1665, (NH) 3333, 3445. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.19 (3H, q, J = 6 Hz, CH_3), 1.73 (3H, s, CH_3), 2.28 (2H, t, J = 6 Hz, CH_2), 3.70 (2H, d, J = 6 Hz, CH_2N) ; 4.83 (2H, s, CH_2 =C), 5.84 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 10.01 (CH_3), 20.34 (CH_3), 29.74 (CH_2), 44.95 (CH_2N), 110.74 (CH_2 =), 142.17 (C=), 173.80 (C=O).

*N-benzyloyl-2,2-dimethylaziridine **(1b)***. IR (CH_2Cl_2, cm^{-1}): ν (C=O) 1675. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.20 (6H, s, $2CH_3$), 2.05 (2H, s, CH_2N), 3.60 (2H, s, CH_2Ph), 7.10-7.25 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 23.69 ($2CH_3$), 36.97 (CH_2N), 41.35 (Cq), 45.22 (CH_2Ph), 126.83 (C, Ph), 127.29 (2C, Ph), 128.62 (2C, Ph), 134.73 (Cq), 181.69 (C=O).

*2-benzyl-5,5-dimethyloxazoline **(2b)***. IR (CH_2Cl_2, cm^{-1}): ν (C=N) 1659. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.28 (6H, s, $2CH_3$), 3.40 (2H, s, CH_2Ph), 3.45 (2H, s, CH_2N), 7.12-7.21 (5H, s, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.83 ($2CH_3$), 43.46 (CH_2Ph), 66.09 (CH_2N), 84.20 (Cq), 126.82 (C, Ph), 128.67 (2C, Ph), 129.10 (2C, Ph), 134.05 (Cq), 166.03 (C=N).

N-(2-hydroxy-2-methylpropyl)-benzylamide ***(3b)***. IR (CH_2Cl_2, cm^{-1}): ν (C=O) 1655, (NH) 3440, (OH) 3580. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.10 (6H, s, $2CH_3$), 3.15 (2H, s, CH_2N), 3.52 (2H, s, CH_2Ph), 3.56 (1H, s, OH), 6.22 (1H, s, NH), 7.20-7.40 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.05 ($2CH_3$), 43.50 (CH_2), 50.47 (CH_2N), 70.51 (Cq), 126.14 (C, Ph), 128.24 (2C, Ph), 128.60 (2C, Ph), 141.73 (C=), 172.20 (C=O).

N-(2-methylprop-2-enyl)-benzylamide ***(4b)***. IR (CH_2Cl_2, cm^{-1}): ν (C=C) 1635, (C=O) 1655, (NH) 3445. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.70 (3H, s, CH_3), 3.55 (2H, s, CH_2Ph), 3.76 (2H, s, CH_2N), 4.75 (2H, s, CH_2 =C), 6.15 (1H, s, NH), 7.15-7.32 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.21 (CH_3), 43.57 (CH_2Ph), 44.90 (CH_2N), 110.47 (CH_2 =), 126.65 (C, Ph), 128.24 (2C, Ph), 127.39 (2C, Ph), 134.82 (Cq), 141.73 (C=), 171.87 (C=O).

N-benzoyl-2,2-dimethylaziridine ***(1c)***. IR (CH_2Cl_2, cm^{-1}): ν 1668 (C=O). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.19 (6H, s, $2CH_3$), 2.20 (2H, s, CH_2N), 7.05-7.85 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.83 ($2CH_3$), 36.62 (CH_2N), 42.30 (C), 127.03 (2C, Ph), 128.24 (2C, Ph), 131.85 (C, Ph), 134.56 (Cq), 178.00 (C=O).

5,5-dimethyl-2-phenyloxazoline ***(2c)***. IR (CH_2Cl_2, cm^{-1}): ν 1670 (C=N). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.36 (6H, s, $2CH_3$), 3.60 (2H, s, CH_2N), 7.16-8.10 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.30 ($2CH_3$), 66.82 (CH_2N), 83.94 (Cq), 126.81 (2C, Ph), 128.52 (2C, Ph), 129.17 (C, Ph), 134.12 (Cq), 166.56 (C=N).

N-(2-methylprop-2-enyl)-benzamide ***(3c)***. IR (CH_2Cl_2, cm^{-1}): ν (C=O) 1666, (NH) 3445, (OH) 3592. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.25 (6H, s, $2CH_3$), 3.32 (1H, s, OH), 3.40 (2H, s, CH_2), 7.11 (1H, s, NH), 7.16-8.10 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.32 ($2CH_3$), 50.73 (CH_2N), 70.95 (Cq), 126.91 (C, Ph), 128.43 (2C, Ph), 128.51 (2C, Ph), 131.55 (C, Ph), 134.60 (Cq), 168.55 (C=O).

N-(2-hydroxy-2-methylpropyl)-benzamide ***(4c)***. IR (CH_2Cl_2, cm^{-1}): ν (C=C) 1635, (C=O) 1655, (NH) 3340, 3450. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.71 (3H, s, CH_3), 3.89 (2H, s, CH_2N), 4.79 (2H, s, CH_2 =C), 6.81 (1H, s, NH), 7.20-7.90 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.32 (CH_3), 45.37 (CH_2N), 110.63 (CH_2 =), 127.22 (2C, Ph), 128.03 (2C, Ph), 131.66 (C, Ph), 137.74 (Cq), 141.94 (C=), 167.75 (C=O).

3. Results and Discussion

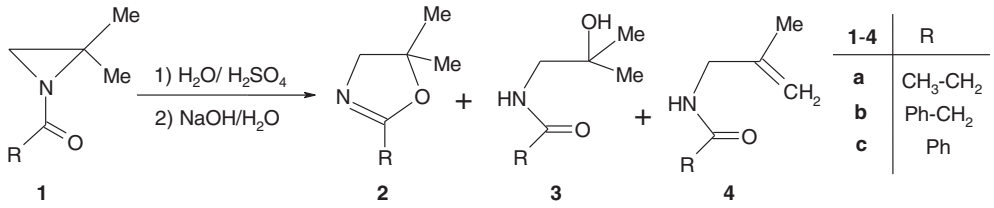
The rearrangements of N-acyl-2,2-dimethylaziridines were carried out under three sets of conditions: a) pure water, b) concentrated sulfuric acid and c) a range of concentrations of aqueous sulfuric acid. The products are oxazolines **2**, amidoalcohols **3** or a mixture of **2**, **3** and methallylamides **4** (table 1, scheme 1).

The second aspect of this study involves the effect of the acyl groups on the outcome of the reaction. We treated three N-acyl-2,2-dimethylaziridines substituted by alkyl groups (ethyl and benzyl) as **1a, 1b** and aryl group (phenyl) as **1c** with a mixture of water and sulfuric acid in different concentrations at room temperature for 96 h.

Such a treatment resulted in the formation of three compounds **2**, **3** and **4** and we conclude that the acid hydrolysis of aziridines **1a-c** with acidified water (39–81%) is more efficient than the acid-activated clay (26–38%) as previously reported.[17,18] In addition, the reaction of N-benzoyl-2,2-dimethylaziridine **1c** with 9% H_2SO_4 by wt. in water leads to a mixture of products **2c**, **3c** and **4c** with a combined yield of 50% which is

Table 1. Transformation of N-acyl-2,2-dimethylazirines **1** by various H_2SO_4/H_2O mixtures into products **2**, **3** and **4** at room temperature.

Entry	Aziridine	X% H_2SO_4 by wt. in water	Total Yield (%)	**2** (%)	**3** (%)	**4** (%)
1	**1a**	0	66	0	66	0
2	**1a**	9	57	14	35	8
3	**1a**	48	39	34	5	0
4	**1a**	98	54	54	0	0
5	**1b**	0	85	0	85	0
6	**1b**	9	81	7	61	12
7	**1b**	48	53	47	6	0
8	**1b**	98	76	76	0	0
9	**1c**	0	91	0	91	0
10	**1c**	9	50	3	42	5
11	**1c**	48	52	27	25	0
12	**1c**	98	87	87	0	0



Scheme 1. Acid hydrolysis rearrangement of N-acyl-2,2-dimethylaziridines **1**.

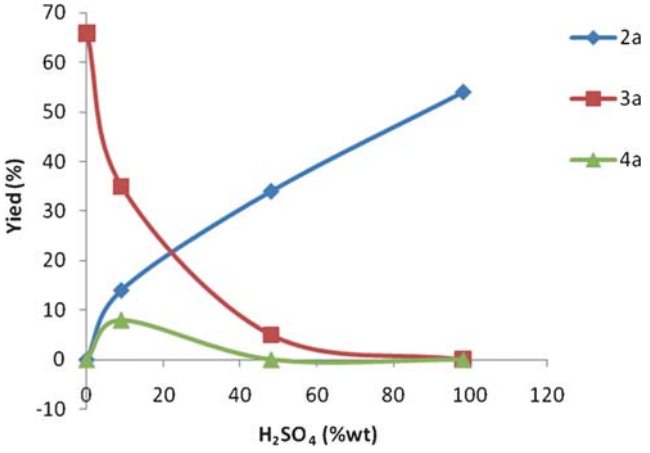


Figure 1. Evolution of the yield of the compounds **2a**, **3a** and **4a** based on X% H_2SO_4 by wt. in water.

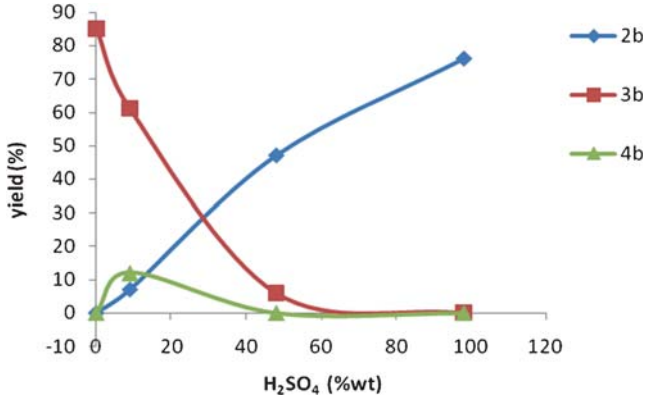


Figure 2. Evolution of the yield of the compounds **2b**, **3b** and **4b** based on X% H_2SO_4 by wt. in water.

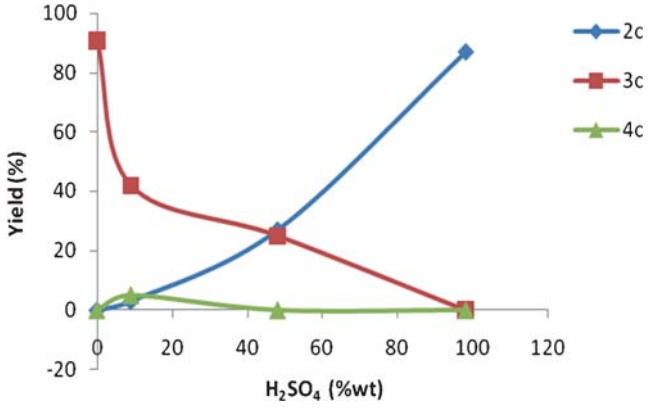


Figure 3. Evolution of the yield of the compounds **2c**, **3c** and **4c** based on X% H_2SO_4 by wt. in water.

much higher than the one obtained by the acid activated clay (30% yield).

This outcome prompted us to extend this type of acid hydrolysis reaction of N-acylaziridines **1** (table 1 and figures 1–3). The selectivity was observed when we used ultrapure water and/or concentrated sulfuric acid to give respectively amidoalcohols **3** (*entries 1, 5 and 9*) and oxazolines **2** (*entries 4, 8 and 12*). We also found that the N-benzoylaziridine **1c** is more reactive than the N-propanoylaziridine **1a** and N-phenylacetyl aziridines **1b**. These experimental results revealed that the mesomeric effect of aroyl group has an important influence in the progress of these reactions.

Furthermore, when the concentration of the solution was equal to a value of 9% H_2SO_4 by wt. in water, we obtained a mixture of oxazolines **2a-c**, amidoalcohols **3a-c** and methallylamides **4a-c** (*entries 2, 6 and 10*).

The formation of methallylamide **4a-c** in aqueous solution at room temperature in 96 hours was totally unexpected. In fact, we have already demonstrated that methallylamides **4** can be obtained by thermolysis of N-acyl-2,2-dimethylaziridines **1** at 110°C in toluene for 48 h.[20]

We also noted that the dehydration of alcohols to alkenes is usually very hard under condition at high temperature. The amidoalcohols **3** can then result by rearrangement of the aziridines **1** in aqueous acid solutions.

Besides, these results also revealed that the increase in acidity of aqueous solution from 9% to 48% H_2SO_4 by wt. leads to a considerable increase in the yield of oxazolines **2** (*entries 2,6,10 vs 3,7,11*). We suggested then that amidoalcohols **3** and methallylamides **4** are rearranged into oxazolines **2** in these conditions. In fact, Fanta obtained 2-paranitrophenyl-5,5-dimethyloxazoline by the treatment of N-methallylparanitrobenzamide with concentrated sulfuric acid at room temperature and confirmed by our research.[21,22] In our study, we obtained oxazoline **2a** by treatment of the amidoalcohol **4a** with 48% H_2SO_4 by wt. in water under the same conditions.[23]

The structures of these products **1-4** were already confirmed by IR, ^{1}H NMR and ^{13}C NMR and also by comparing its authentic samples.[19]

Similarly, we followed the evolution of product formation based on the X% H_2SO_4 by wt. in water. The analysis of the curves presented in figures 1–3 reveals that the allylamides **4a-c** were formed with low yields and at low concentrations and then disappear starting from 48% of the total weight and that there are two critical points at 21% and 29% in yields. We found that these products **2a**, **2b** and **3a**, **3b** were obtained using 21% and 24% H_2SO_4 by wt. in water. However, the replacement of ethyl and benzyl groups by phenyl group stabilizes the aziridine **1c** and that requires a double concentration of 48% H_2SO_4 by wt. in water to form the products **2c** and **3c** (27 and 25% yields).

On the other hand, several experimental and theoretical works focused on the determination of the structures of aziridines and the study of the reactivity of these heterocycles.[26–30]

DFT quantum chemical calculations of structures and energies were carried out with the aid of GAUSSIAN 09 set of programs.[29] Geometrical parameters of the reactants and products for the studied reactions were fully optimized at the hybrid density functional B3LYP[30,31] level using the 6-311++G(2d,2p) basis.

A good agreement is obtained between the experimental and the theoretical results. The results show that the two carbons of methyl groups carried by the C2 carbon of aziridines **1** have atomic charges higher than those of C2 and C3 (tables 2–4, *entries 1-3*).

Table 2. Evolution of atomic charges (a.u.) of selected atoms of compounds **1a, 2a**, **3a** and **4a.**

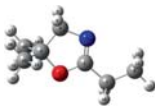
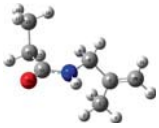
Entry	Atom	 **1a**	 **2a**	 **3a**	 **4a**
1	$\underline{C}H_3$	−0.6	−0.6	−0.6	−0.6
2	$\underline{C}H_3$	−0.6	−0.6	−0.6	
3	$\underline{C}H_2$	0.1	−0.2	−0.2	−0.2
4	$\underline{C}$-Me	−0.2	0.3	0.3	0.0
5	N	−0.5	−0.5	−0.6	−0.6
6	C-$\underline{O}$		−0.6		
7	C=$\underline{O}$	−0.6		−0.7	−0.6
8	$\underline{C}$=O	0.7		0.7	0.8
9	$\underline{C}$=N		0.6		
10	C=$\underline{N}$		−0.5		

Table 3. Evolution of atomic charges (a.u.) of selected atoms of compounds **1b**, **2b**, **3b** and **4b**.

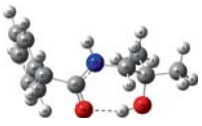
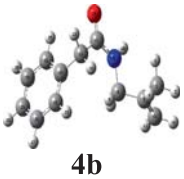
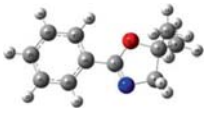
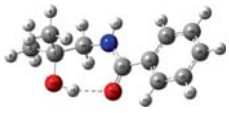
Entry	Atom	 **1b**	 **2b**	 **3b**	 **4b**
1	$\underline{C}H_3$	−0.6	−0.6	−0.6	−0.6
2	$\underline{C}H_3$	−0.6	−0.6	−0.6	
3	$\underline{C}H_2$	0.1	−0.2	−0.2	−0.2
4	$\underline{C}$-Me	−0.2	0.3	0.3	0.0
5	$\underline{N}$	−0.5	−0.5	−0.6	−0.5
6	C-$\underline{O}$		−0.6		
7	C=$\underline{O}$	−0.6		−0.7	−0.6
8	$\underline{C}$=O	0.7		0.7	0.8
9	$\underline{C}$=N		0.6		
10	C=$\underline{N}$		−0.5		

Table 4. Evolution of atomic charges (a.u.) of selected atoms of compounds **1c**, **2c**, **3c** and **4c**.

Entry	Atom	 **1c**	 **2c**	 **3c**	 **4c**
1	$\underline{C}H_3$	−0.6	−0.6	−0.6	−0.6
2	$\underline{C}H_3$	−0.6	−0.6	−0.6	
3	$\underline{C}H_2$	0.2	−0.2	−0.2	−0.2
4	$\underline{C}$-Me	−0.1	0.3	0.3	0.0
5	$\underline{N}$	−0.5	−0.5	−0.6	−0.6
6	C-$\underline{O}$		−0.6		
7	C=$\underline{O}$	−0.6		−0.7	−0.5
8	$\underline{C}$=O	0.7		0.7	0.7
9	$\underline{C}$=N		0.6		
10	C=$\underline{N}$		−0.5		

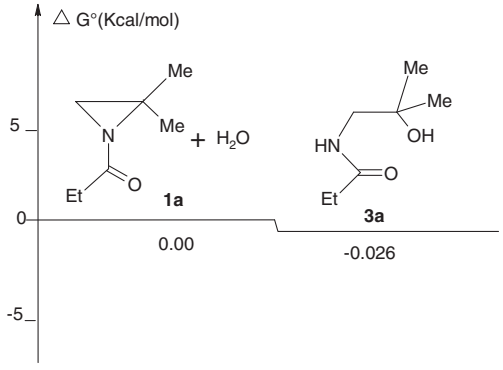


Figure 4. Energetic profile of hydrolysis of N-propanoyl-2,2-dimethylaziridine **1a**.

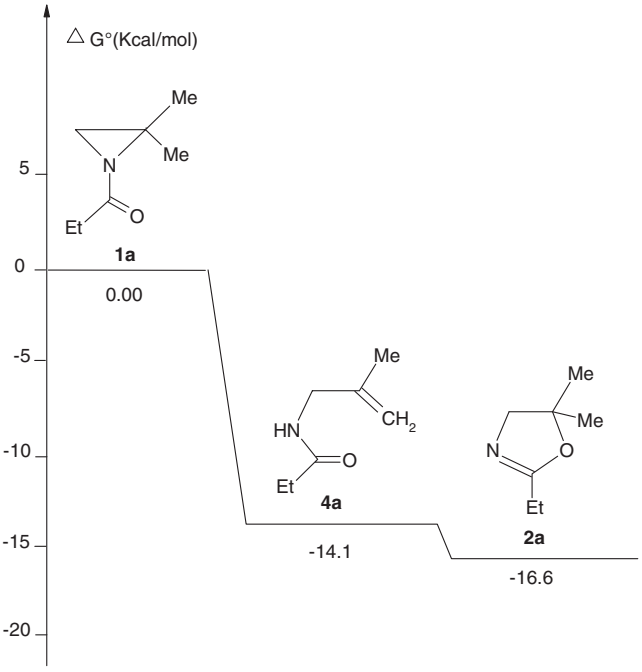


Figure 5. Energetic profile of isomerization of N-propanoyl-2,2-dimethylaziridine **1a.**

In the case of reagents **1**, we noticed that the atomic charge of oxygen is far superior to that of nitrogen (tables 2–4, *entries 5,7*). Consequently, we conclude that the oxygen site is more basic than the nitrogen one. However, the nitrogen site is more nucleophilic site than the oxygen site, the protonation of the aziridine occurs on the nitrogen atom. We have also observed a very important difference in charge density between oxygen and nitrogen when comparing the atomic charges of C=O and C=N groups of compounds **1-4** (tables 2–4, *entries 9, 10*).

All results are presented in figures 4–9 where we have plotted the energies of the reactant and products. A good agreement is obtained between the experimental and the theoretical. Figures 4, 6 and 8 showed that the transformation of N-acylaziridine **1a-c** into amidoacohol **3a-c**. The formation of amidoalcohol **3** took place at low sulfuric acid concentration (9% wt.), while at higher concentration (48% wt.) the reaction afforded oxazoline **2** and allylamide **4**. The latter compound **4** was very unstable in acidic medium and instantly transformed into its corresponding oxazoline **2** isomer.

We conclude that the kinetic behavior of the acid hydrolysis of aziridines **1a-c** depends closely on the nature of acyl group carried by the heterocycle.

Several mechanisms in acidity media were proposed to explain the formation of the mixture of three products **2**, **3** and **4** from N-acyl-2,2-dimethylaziridine **1**.

Firstly, we have proposed "a push pull" mechanism to explain the formation of amidoalcohol **3** by neutral hydrolysis of the N-acylaziridines **1** (scheme 2). That it is a facile formation of a hydrogen

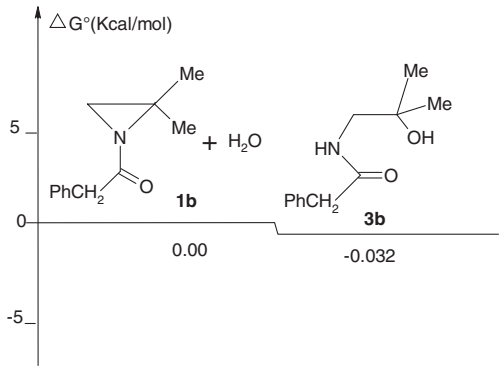


Figure 6. Energetic profile of hydrolysis of N-phenylacetyl-2,2-dimethylaziridine **1b**.

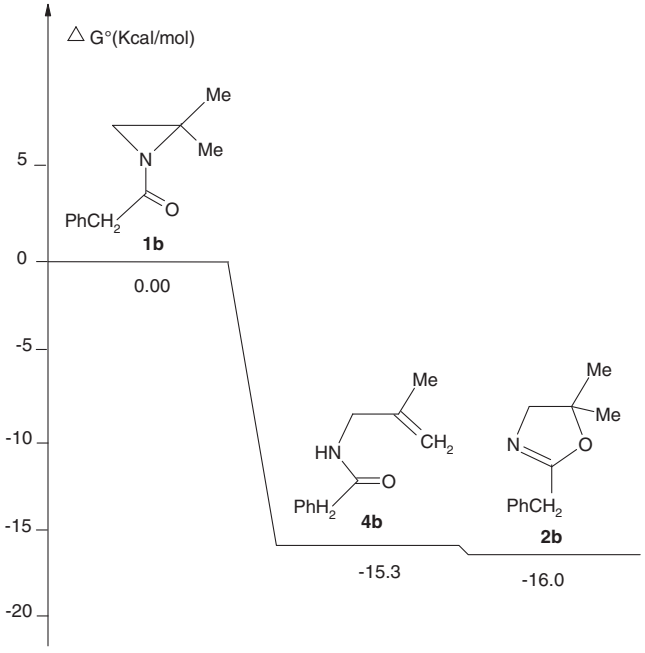


Figure 7. Energetic profile of isomerization of N-phenylacetyl-2,2-dimethylaziridine **1b**.

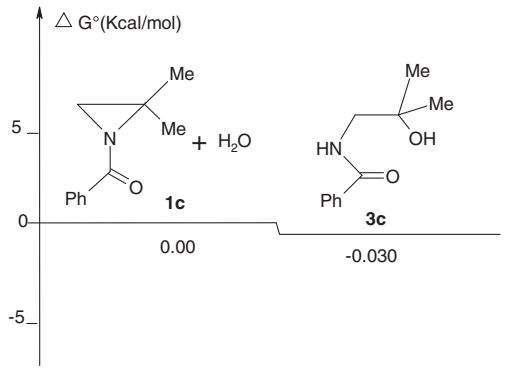


Figure 8. Energetic profile of hydrolysis of N-benzoyl-2,2-dimethylaziridine **1c**.

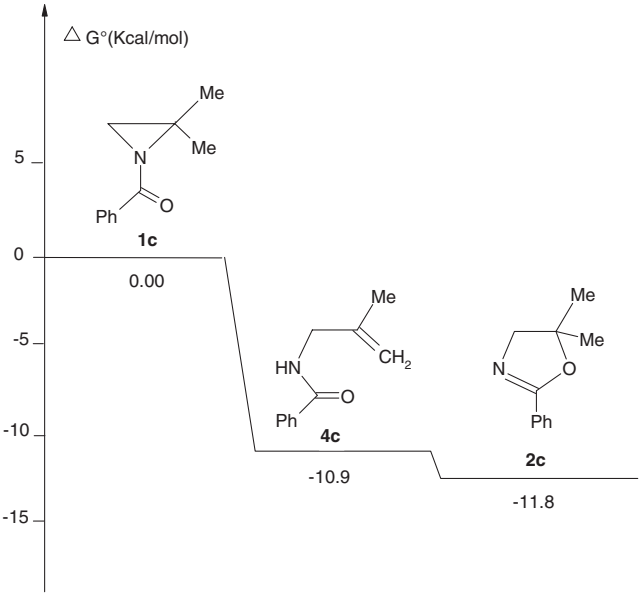


Figure 9. Energetic profile of isomerization of N-benzoyl-2,2-dimethylaziridine **1c**.

bond between the first water molecule and the oxygen of the amide group or bond of aziridine **1** to give the intermediate **I**. The regiospecific nucleophilic attack of the second water molecule happens on the C2 carbon, best suited with a positive partial charge, which is stabilized by the density effects of the methyl groups. The oxonium intermediate **II** leads to the amidoalcohol **3** after proton exchange and rearrangement of the intermediate **III** (scheme 2).

Furthermore, the use of concentrated sulfuric acid favors the oxophilic reaction of the substrate **1** to lead to N-protonated **IV** (scheme 3). This intermediate **IV** undergoes the heterolytic cleavage of the C2-N bond to give the more stable tertiary carbocation **V**. The ring closure of **V**, by nucleophilic attack of oxygen on this tertiary carbocation, forms the oxazoline **2** *via* the intermediate **VI**.

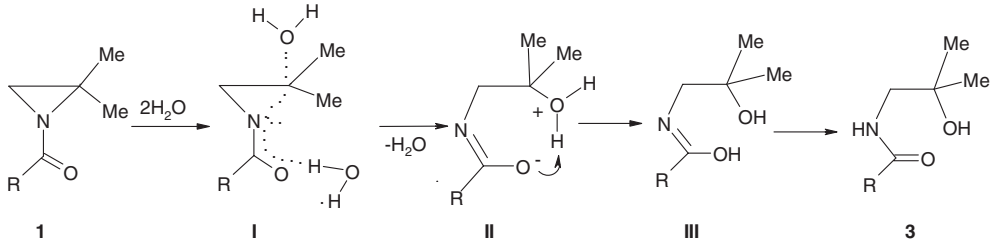
The treatment of N-acyl-2,2-dimethylaziridine **1** with aqueous acidic solution (9% and 48% by weight), can be explained as follows: the first step is the formation of the aziridinium ion **IV** and second step is obtaining the carbocation **V** (scheme 4). The last intermediate **V** undergoes the competition between hydrolysis and rearrangement. Indeed, the rearrangement is performed by the migration of the hydrogen from the methyl group on the oxygen of amide on a transition state **TS1**, to give the intermediate **VII** (figure 4, path a). The latter **VII** will undergo either the intramolecular cyclization to give the oxazoline **2** through the transition state **TS2** and the intermediate oxazolinium **IV** (scheme 4, path c) or undergo proton exchange for allylamide **4** (scheme 4, path d). Furthermore, solvation of the intermediate **V** with two molecules of water leads to the transition state **TS3** which will be transformed into amidoalcool **3**

by proton exchange of the intermediate **IX** (scheme 4, path b).

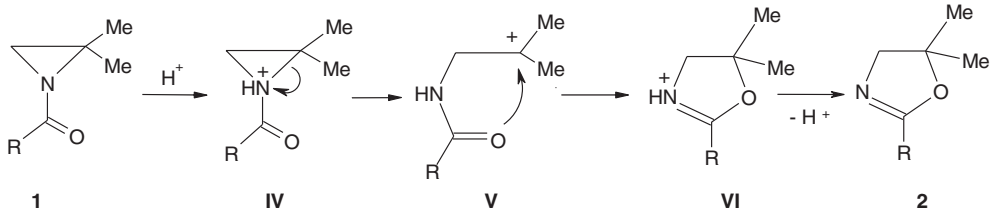
For a good understanding of the acid hydrolysis process of these heterocycles **1**, we focused our study on the reactivity of the N-propanoyl-2,2-dimethylaziridine **1a** in acidic medium. In the first step of this theoretical study, we carried out the geometry optimization calculations, the molecular structure starting from the carbocation **Va** and moving along the coordinate of the reaction until the oxazolinium **IVa**. The results of these IRC show that rearrangement through two transition states **TS1a** (9.02 kcal mol^{-1}) and **TS2a** (20.86 kcal mol^{-1}).

The analysis of the energetic plots are shown in figures 5 and 10 and the mechanism is shown in scheme 4 which reveal that the methallylamide **4a** is the kinetic product, whereas the oxazoline **2a** is the thermodynamic product.

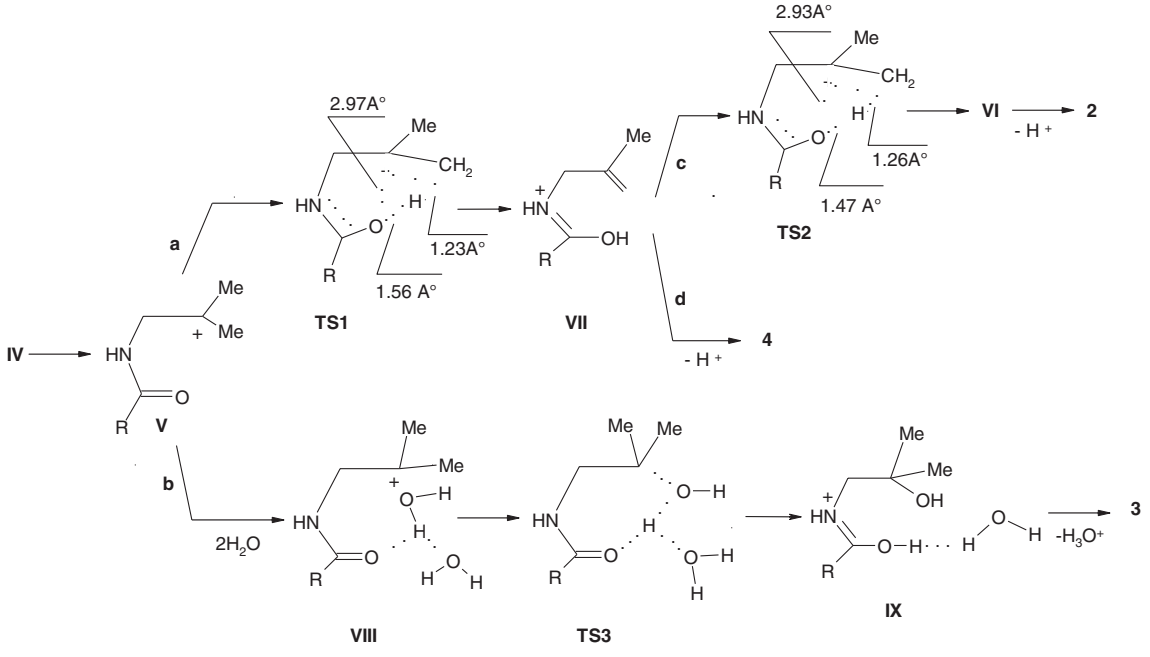
In the second step, we followed the rearrangement of this intermediate **Va** into the amidium **IX** by the



Scheme 2. Mechanism proposed of the neutral hydrolysis of N-acylaziridine **1**.



Scheme 3. Mechanism proposed of the acid isomerization of N-acylaziridine **1**.



Scheme 4. Proposed competitive rearrangements of the acid hydrolysis of N-acylaziridine **1**.

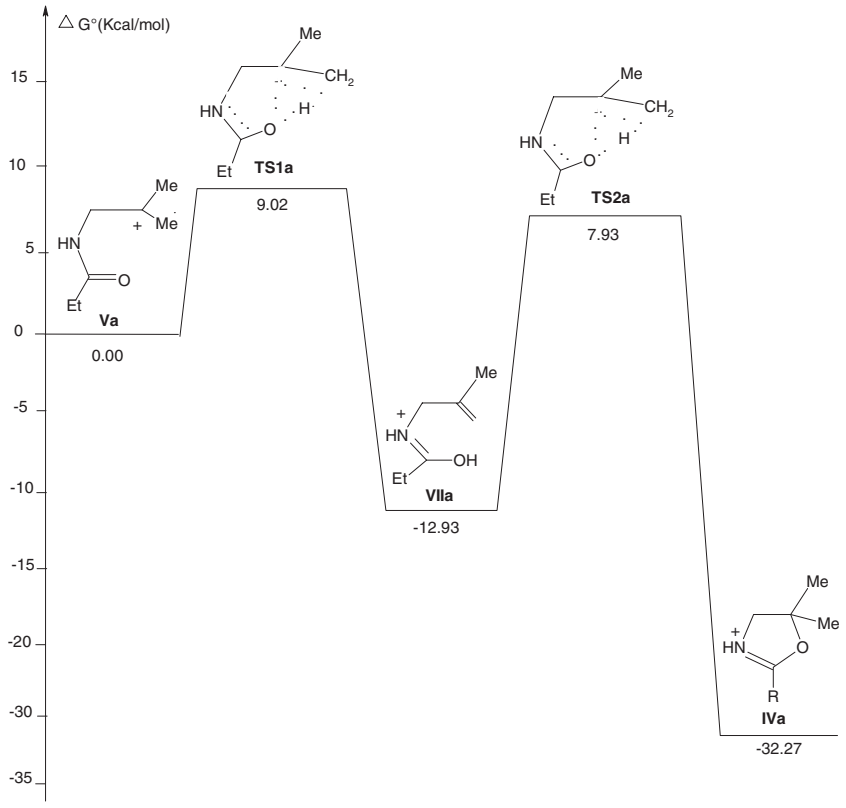


Figure 10. Energetic profile for paths a, c and d of rearrangement of the intermediate **Va**.

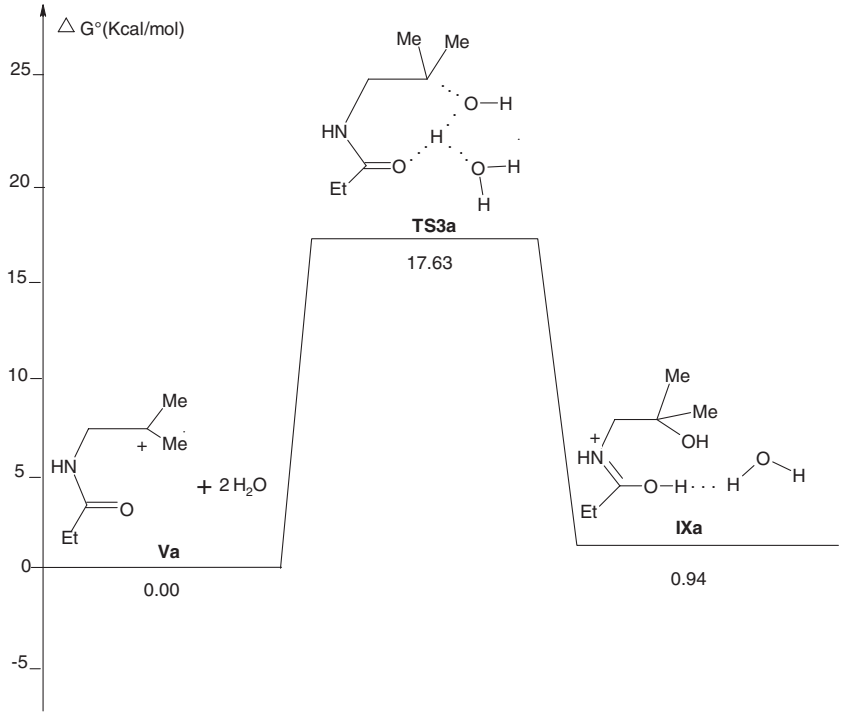
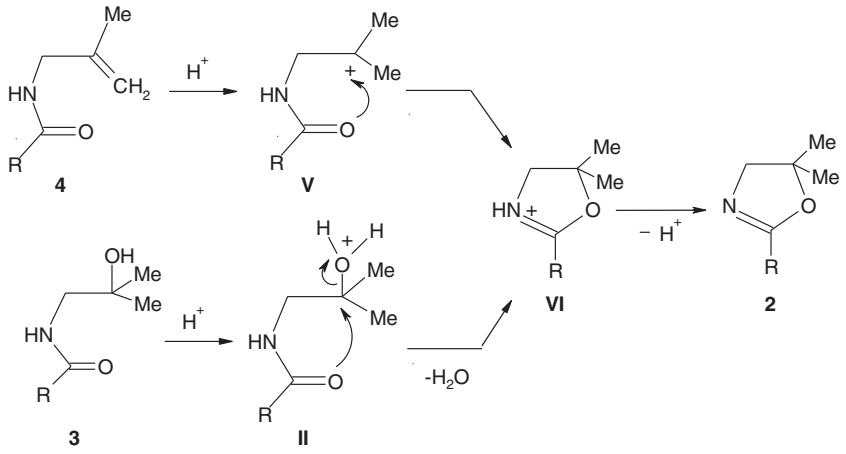


Figure 11. Energetic profile for path b of rearrangement of the intermediate **Va**.



Scheme 5. Mechanism of acid transformation of amidoalcohol **3** and allylamide **4** into oxazoline **2**.

calculation of the IRC (figure 11). The results show that this reaction involves a transition state **TS3a** (17.63 kcal mol^{-1}).

On the other hand, we have found that increasing the concentration of sulfuric acid causes the transformation of amidoalcool **3** and allylamide **4** into oxazoline **2** (table 1). We proposed then the following mechanism (scheme 5).

4. Conclusions

In conclusion, this work illustrates complementarities between theoretical study and chemical reactions to determine the mechanism of formation of the compounds **2**, **3** and **4**. The evolution of the yields of oxazolines **2**, amidoalcohols **3** and methallylamides **4** closely depended on both the acidity of the reaction medium and the nature of the acyl group of 2,2-dimethylaziridines **1**.

Supplementary Information (SI)

^{1}H and ^{13}C NMR spectra of representative molecules are available at www.ias.ac.in/chemsci.

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