

Organic & Supramolecular Chemistry

[2 + 2] Cycloadditions of Sorbyl Tosylate with Imines/1-Azadienes: A One-Pot Domino Approach for α -Alkylidene- β -lactams and Their Computational Studies and Antimicrobial Evaluation

Yogesh Kumar,^[a, b] Preet Mohinder Singh Bedi,^[c] Prabhpreet Singh,^[d] Adebayo A. Adeniyi,^[e] Ashona Singh-Pillay,^[f] Parvesh Singh,^[f] and Gaurav Bhargava^{*[a]}(Dedicated to Prof. M. P. Mahajan on the occasion of his 71st Birthday)

The manuscript describes a straightforward and atom-efficient method for the synthesis of α -alkylidene- β -lactams using sorbyl tosylate and imines/1-azadienes at high temperature (80 °C). The Density functional theory calculations have shown the prevalence of the first order kinetics in these [2 + 2] cyclo-

additions to produce mixture of 3-butadienyl-azetidin-2-ones and 3-but-2-enylidene-azetidin-2-ones in good yields. The 3-but-2-enylidene-azetidin-2-ones have also shown antimicrobial activity against the *E. coli*, *S. aureus*, *P. aeruginosa*, *B. cereus* and *B. subtilis*.

Introduction

Ketenes are versatile intermediates in organic synthesis.^[1] There are numerous reports on synthesis and cycloadditions of functionalized ketenes for the synthesis of heterocyclic systems of biological relevance.^[2–3] The [2 + 2] cycloadditions of ketenes with alkenes or iminic systems have widespread been utilized for the synthesis of carbo- and heterocyclic systems respectively.^[3] There has been significant interest and controversies over the mechanism of ketene-imines cycloadditions. Experimental work as well as theoretical studies have been made on the reactions of the imines with simple ketenes.^[4] It is well understood that the Staudinger reactions involving [2 + 2]

cycloadditions of ketene and imines are proceeded *via* zwitterionic intermediates as shown in the Figure 1.^[5]

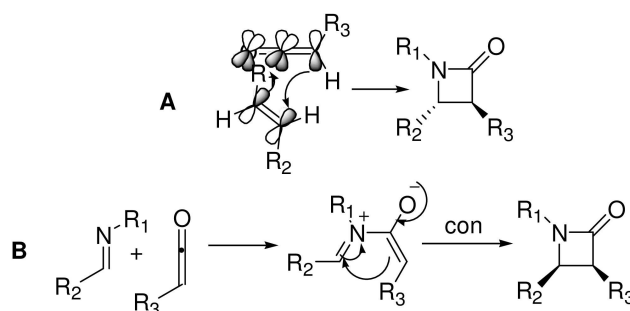


Figure 1. (A) Orbital Interactions in concerted cycloaddition. (B) Stepwise mechanism. con = conrotatory

[a] Dr. Y. Kumar, Dr. G. Bhargava

Department of Chemical Sciences, I. K. Gujral Punjab Technical University, Kapurthala, Punjab-144603, India
E-mail: gauravorganic@gmail.com

[b] Dr. Y. Kumar

UNAM–National Nanotechnology Research Center, Institute of Materials Science and Nanotechnology, Department of Chemistry, Bilkent University, 06800 Turkey

[c] Dr. P. M. S. Bedi

Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143005, India

[d] P. Singh

Department of Chemistry, Guru Nanak Dev University, Amritsar-143005, India

[e] A. A. Adeniyi

Pharmacy Department, University of KwaZulu Natal, Westville Campus, Durban, Chemistry Department, University of Oye-Ekiti, Ekiti State, Nigeria

[f] A. Singh-Pillay, Dr. P. Singh

School of Chemistry and Physics, University of KwaZulu Natal, P/Bag X54001, Westville, Durban 4000, South Africa
E-mail: singhp4@ukzn.ac.za

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However, the corresponding studies on [2 + 2] cycloaddition reactions involving conjugated ketene such as butadienylketene still need to be explored. Earlier Mahajan *et al.* have explored the [2 + 2] and [4 + 2] cycloaddition reactions of butadienylketene generated *in situ* from sorbyl chloride and triethylamine, with imines and 1,3-diazabuta-1,3-dienes respectively.^[6] The reaction resulted in the formation of *cis*- and *trans*-butadienyl-azetidin-2-ones. However, studies on cycloaddition reactions involving butadienylketene with iminic systems at high temperature and using alternative methods for *in situ* generation of butadienylketene still need to be studied. On the other hand, α -alkylidene- β -lactams are known structural units found in several potent β -lactamase inhibitors such as Ro 15–1903, asparenomyins, 6-(2'-pyridyl)methylene penem sulfone,

and 6-[(Z)-methoxymethylidene]penicillanic acid.^[7] 4-Alkylidene- β -lactams have recently been reported for activity against human leukocyte elastase, gelatinase MMP-2, and MMP-9.^[8-9] 6-Alkylidene-penicillanate sulfones and sulfoxides have antitumor properties.^[9] Moreover, α -alkylidene- β -lactams have also been explored for the preparation of β -lactam antibiotics,^[10] β -amino alcohols and acids.^[11] Besides this, α -alkylidene- β -lactams have provided important intermediates for synthesis of α -keto- β -lactams, spiro- β -lactams and bicyclic- β -lactams.^[12]

Earlier reported methods for preparation of α -alkylidene- β -lactams^[13-18] have cumbersome multistep reaction procedures and involve the use of toxic metals (Figure 2). In view of

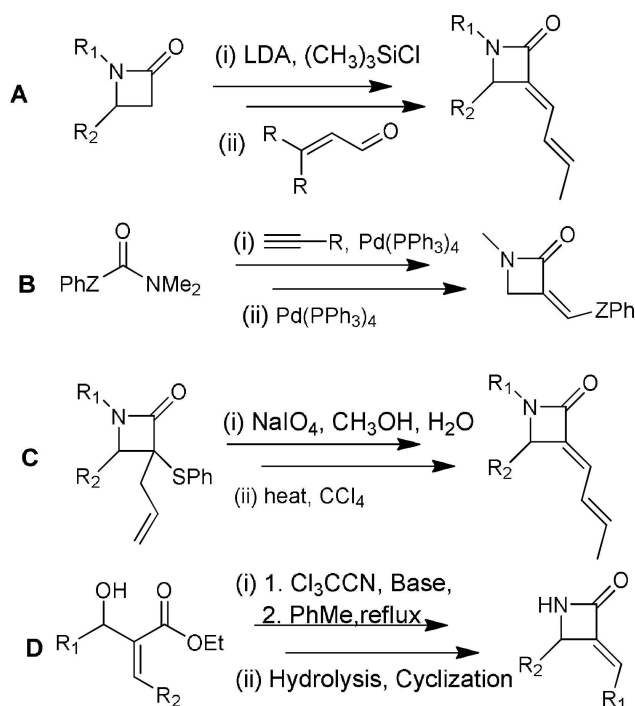


Figure 2. Previous reports on synthesis of α -alkylidene- β -lactams

previous reports and our ongoing interests in heterocyclic chemistry,^[19] we have explored the reactions of butadienylketene generated *in situ* from sorbyl ketene with variety of imines at high temperature (80°C).^[6,20-23] The reactions resulted in the formation of mixture of cycloadducts with α -alkylidene- β -lactams i.e. but-2-en-1-ylidene-azetidin-2-one as major adduct. The current methodology is useful in terms of facile, high yields, short steps and without the use of toxic reagents for the synthesis of α -alkylidene- β -lactams.

Results and Discussion

We, initially, investigated the reactions of imines **1a** with butadienyl ketene generated *in situ* from sorbic acid **2** in solvents at different reaction temperatures; the results of these experiments are tabulated in Table 1. The common solvents such as toluene, xylene and 1,2-dichloroethane were selected

Table 1. Optimization of Reaction conditions.

Entry	Solvent	Temp (°C)	Yield (%) ^a	4/3 ^b
1	Dichloroethane	rt	30	0:10
2	Xylene	rt	30	0:10
3	Toluene	rt	20	0:10
4	DCM	rt	20	0:10
5	Dichloroethane	40	45	1:9
6	Xylene	40	35	1:9
7	Toluene	40	20	0:10
8	Dichloroethane	60	60	4:6
9	Xylene	60	45	3:7
10	Dichloroethane	80	75	4:1
11	Xylene	80	55	7:3

^aOverall Isolated yield. ^bRatio of 4 : 3(from Crude ¹HNMR)

for their comparative effects on the synthesis of α -alkylidene- β -lactams in their [2+2] cycloaddition reactions at different temperatures (Table-1).

Interestingly, the use of polar aprotic solvents (DCE) at different temperatures, invariably promoted the formation of **4a** and there is decrease in yield of **4a** when reactions were conducted in non polar solvents such as toluene and xylene. Best results in terms of yields were observed using 1,2-dichloroethane as solvent at 80 °C (75%, Table-1; entry 10). The yields of **4a** were decreased at low temperatures and dienyl-2-azetidinones **3a** were formed as major adduct. However, the reactions of imine **1a** in xylene at 80°C, resulted in the reasonable yields of the corresponding lactam **4** (upto 55%, Table 1; entry 11).

After optimization of reaction conditions, [2+2] cycloaddition reactions of diversely substituted imines **1a-h** were explored with butadienylketene generated *in situ* from sorbic acid and tosyl chloride in the presence of triethylamine. The reaction resulted in formation of 3-(buta-1,3-dien-1-yl)azetidin-2-one **3** and 3-(but-2-en-1-ylidene)azetidin-2-one **4** in varying ratios. Best conditions in terms of yield and selectivity of 3-(but-2-en-1-ylidene)azetidin-2-ones **4** were observed using imine **1b** derived from *p*-toluidine in these [2+2] reactions (Table 2; Entry 2).

The reactions of sorbyl chloride were further studied with 1-azadiene **5** derived from cinnamaldehyde and aromatic amines at high temperature (80°C).The reactions resulted in the formation of 3-(but-2-en-1-ylidene)-4-styrylazetidin-2-ones **6** in good yield and the formation of 3-(buta-1,3-dien-1-yl)-4-styryl-azetidin-2-ones were not observed (Table 3).

The functionalized 3-but-2-enylidene-azetidin-2-ones **4**, thus obtained were characterized on the basis of analytical and spectral evidences. The detailed information is provided in the supporting information and the salient features are discussed here. The compound, 3-(but-2-en-1-ylidene)-4-phenyl-1-(*p*-tolyl)azetidin-2-one **4b** for example, analyzed for C₂₀H₁₉NO, IR

Table 2. Synthesis of 3-but-2-enylidene-1,4-diaryl-azetidin-2-one **4**.

Entry	R ₁	R ₂	Product	Xylene 80 °C		DCE ^a 80 °C	
				Yield ^b (%)	Yield ^b (%)	3	4
1.	-C ₆ H ₅	-C ₆ H ₅	3 a/4 a	16	39	15	60
2.	<i>p</i> -CH ₃ -C ₆ H ₄	-C ₆ H ₅	3 b/4 b	18	42	15	62
3.	<i>p</i> -Cl-C ₆ H ₄	-C ₆ H ₅	3 c/4 c	14	34	12	48
4.	<i>p</i> -OCH ₃ -C ₆ H ₄	-C ₆ H ₅	3 d/4 d	15	34	11	46
5.	-C ₆ H ₁₁	-C ₆ H ₅	3 e/4 e	13	32	13	52
6.	-C ₆ H ₅	<i>p</i> -Cl-C ₆ H ₄	3 f/4 f	14	32	10	40
7.	<i>p</i> -CH ₃ -C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	3 g/4 g	14	33	11	45
8.	<i>p</i> -Cl-C ₆ H ₄	<i>p</i> -Cl-C ₆ H ₄	3 h/4 h	12	29	10	41

^aDichloroethane. ^bIsolated yield after purification

Table 3. Synthesis of 3-(but-2-en-1-ylidene)-4-styrylazetidin-2-one **6**.

Entry	R	Conditions	Product	Yield (%) ^a
1.	-C ₆ H ₅	DCE, 80 °C	6 a	60
2.	<i>p</i> -CH ₃ -C ₆ H ₅	DCE, 80 °C	6 b	55

^aIsolated yield after purification.

spectrum showed strong absorption peaks at 1736 cm⁻¹ corresponding to the carbonyl group of 2-azetidinone. The high resolution ¹HNMR (500 MHz) spectrum showed a characteristic doublet at δ 6.68 having *J* = 11.5 Hz corresponding to H⁵, a doublets of doublet at δ6.00 (*J* = 7 Hz, 15 Hz) corresponding to H⁷, a doublets of doublets of doublet at δ5.84 (*J* = 1.5 Hz, 11.5 Hz, 15 Hz, 26 Hz) assigned to H⁶, and a singlet at δ5.45 assigned to H⁴ of the lactam ring. The presence of 15 Hz coupling between H⁶ and H⁷ confirms the *trans* geometry around C-6 and C-7 double bond. The presence of 11.5 Hz coupling around H⁵ and H⁶ further confirms the *cis*-stereochemistry of H⁵ and H⁶ proton. The ¹³CNMR has shown the presence of one carbonyl carbon at δ 162.01, C⁴ carbon of lactam ring at δ 63.02 and dienyl chain at δ 136.82, 138.94, 139.17, 18.74 (CH₃).

The reactions of sorbyl chloride were further studied with 1-azadiene **5** derived from *trans*-cinnamaldehyde and aromatic amines at high temperature (80 °C). The reactions resulted in the formation of 3-(but-2-en-1-ylidene)-4-styrylazetidin-2-ones **6** in good yield and the formation of 3-(buta-1,3-dien-1-yl)-4-styrylazetidin-2-ones were not observed (Table 3).

The interconversions between 3-(buta-1,3-dien-1-yl)-azetidin-2-one **3a** and 3-(but-2-en-1-ylidene)-azetidin-2-one **4a** were

also attempted under different reaction conditions using even higher concentrations of base and at higher temperature (80 °C). These interconversions were unsuccessful and the starting material was recovered. This confirms the occurrence of alternative mechanistic routes for the formation of 3-(buta-1,3-dien-1-yl)-azetidin-2-one **3a** and 3-(but-2-en-1-ylidene)-azetidin-2-one **4a**

Computational Results

In order to support the experimental observations, the density functional theory calculations were employed. The optimized geometries of compounds **3** and **4** are shown in Figure 3. The

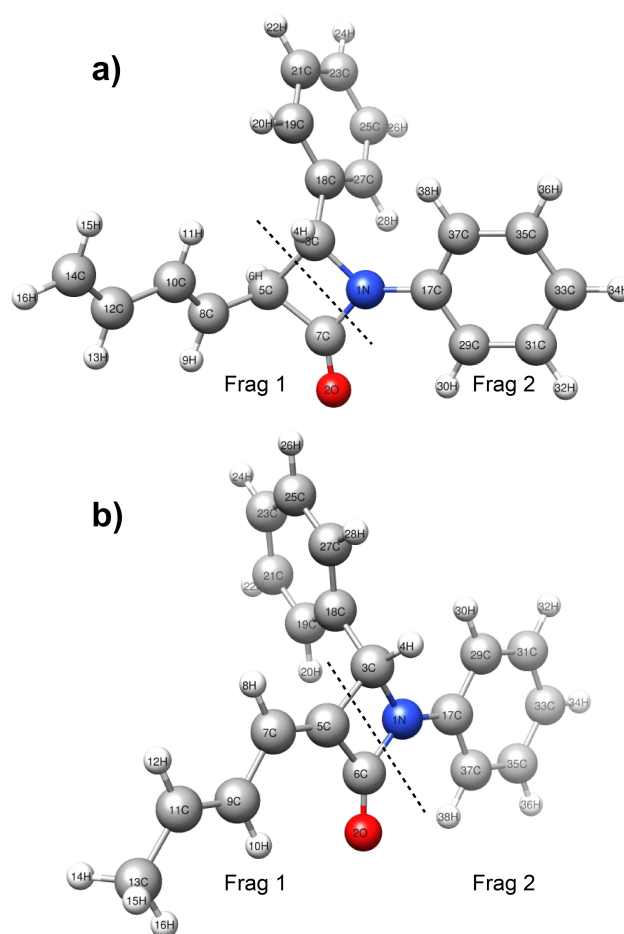


Figure 3. The optimized geometries of a) lactam **3** and b) lactam **4** with the numbering of the atoms and the line showing the plane of the fragments

thermodynamic and kinetics properties were obtained from the optimized geometries of the reactants, product and transition state structures.^[24–30] Applying the Arrhenius equation as indicated below, the enthalpy (*H*) values were used to compute the kinetic energy while free energy (*G*) values were used by using transition-state-theory (Eyring equation) as shown in the expressions below:

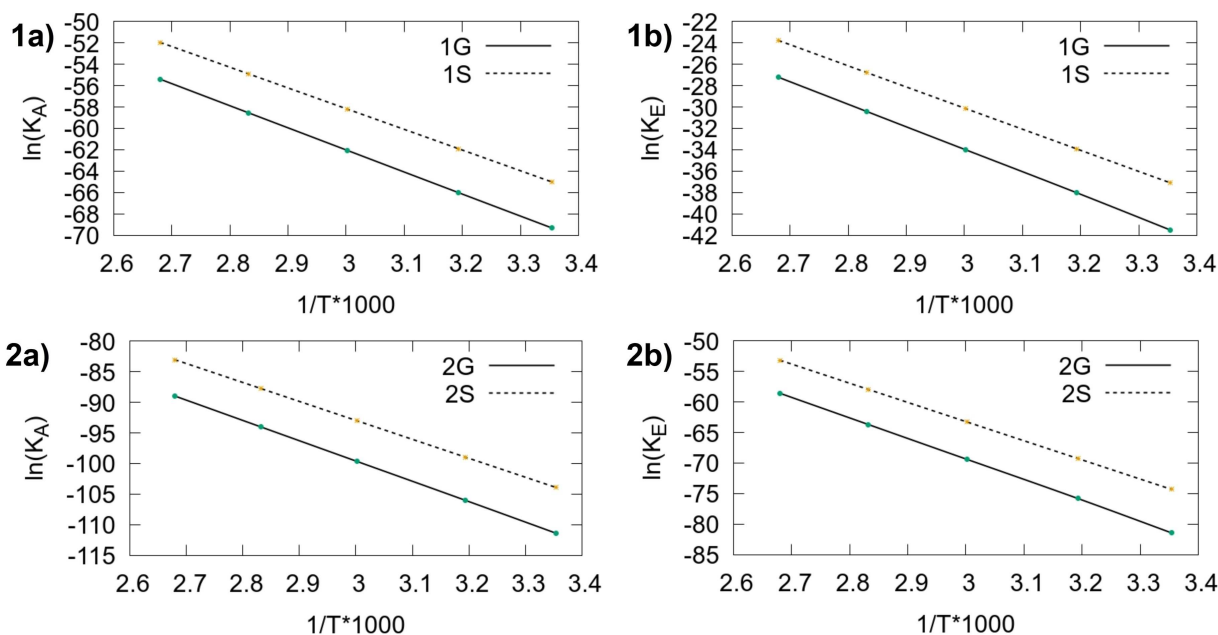


Figure 4. The forward reaction constant using a) Arrhenius b) Eyring for gas phase (G) and solvent medium (S) of lactam 3 and 4 starting from reactants to product.

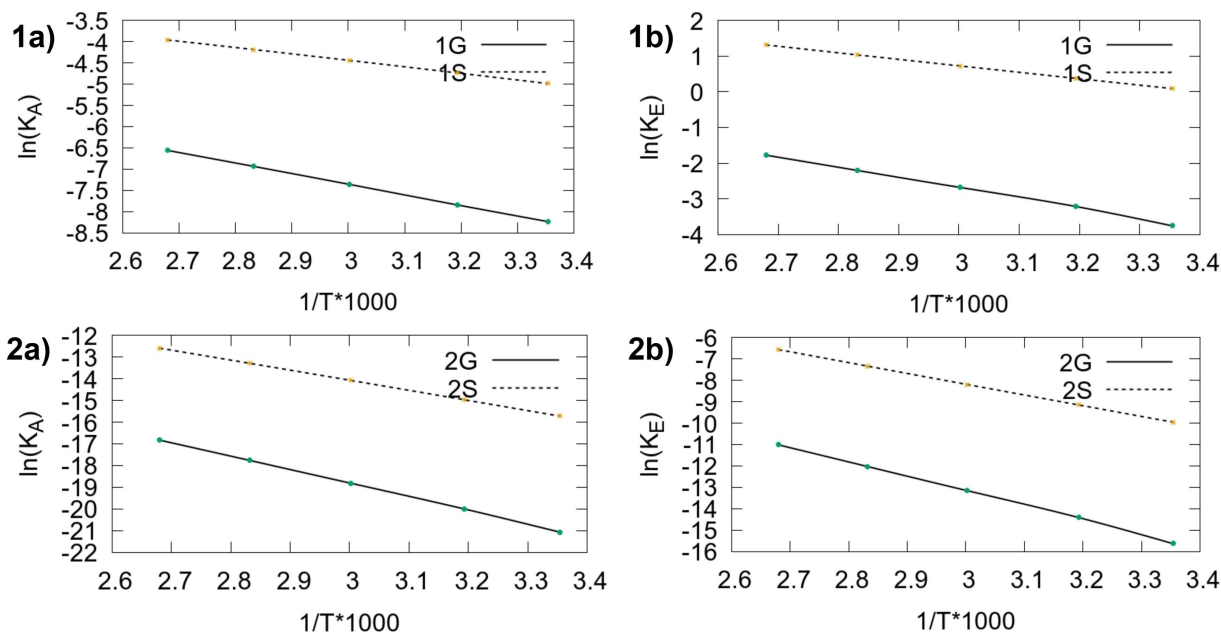


Figure 5. The reverse reaction constant using a) Arrhenius b) Eyring for gas phase (G) and solvent medium (S) of lactam 3&4 starting from product back to reactants.

$$k = A \exp\left(\frac{-\Delta E_a^\ddagger}{RT}\right) \text{ (Arrhenius equation)}$$

$$k = \frac{K_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right) \text{ (Eyring equation)}$$

The thermodynamic properties and kinetics were computed at temperature of 298.15, 313.15, 333.15, 353.15 and 373.15 K

in gas phase and also in solvent dichloromethane. The reaction is assumed as first order reaction as evident from the linear relation between the $\ln K$ and the inverse values of temperature (Figure 2 and 3).

Using both the Arrhenius and Eyring methods, it is very clear that the solvent medium (dichloroethane) significantly enhances the kinetics of the forward reaction (Figure 4) but have little effects on the reverse reaction (Figure 5). In either gas

phase (1G or 2G) or solvent medium (1S or 2S), the reverse reaction is kinetically unfavourable as compared to forward reaction.

The reaction for the formation of lactam 3 is kinetically more favourable than lactam 4 (Figure 4) while the reactions of lactam 4 is thermodynamically more favourable as shown in Figure 6. The solvent employed does not increase the

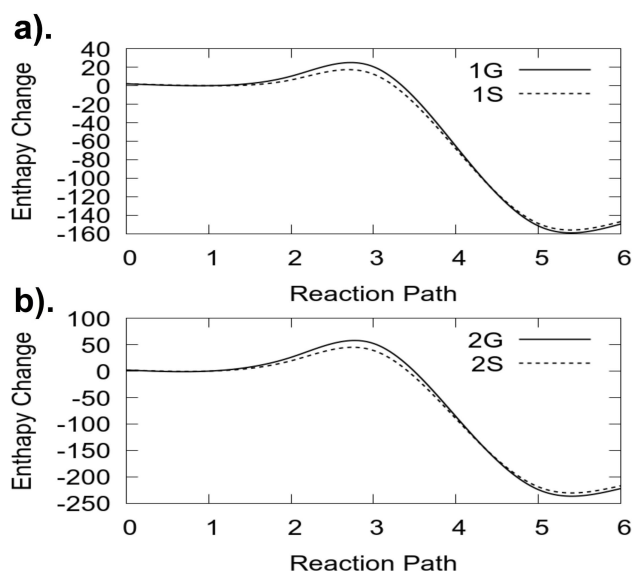


Figure 6. The energy reaction pathway of the compounds a) 3 and b) 4 at the temperature of 298.15 K in gas phase (G) and solvent medium (S).

thermodynamics of the reaction and only enhances the kinetics of reaction. The solvent medium also significantly enhances the entropy of lactam 4 as shown in Figure 7 which increases

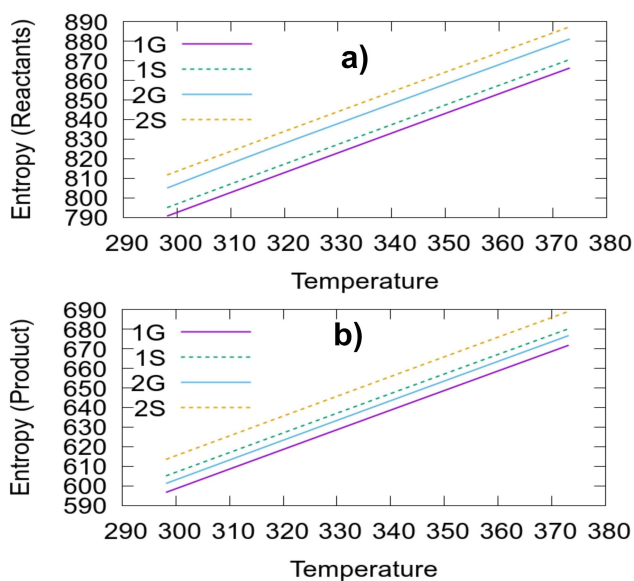


Figure 7. The energy reaction pathway of the compounds a) 3 and b) 4 at the temperature of 298.15 K in gas phase (G) and solvent medium (S).

linearly as temperature increases. These results suggest that the formation of lactam 4 is more favourable than lactam 3 especially at higher temperature.

Reaction Path Properties

Making use of the Natural Resonance Theory (NRT) methods for the analysis of the transition state structures, the reaction path was studied using the bond distance N_1-C_7 in lactam 3 and N_1-C_6 in lactam 4.^[31] The average weights of the reactants and the product along the reaction path are shown in Figure 8. As

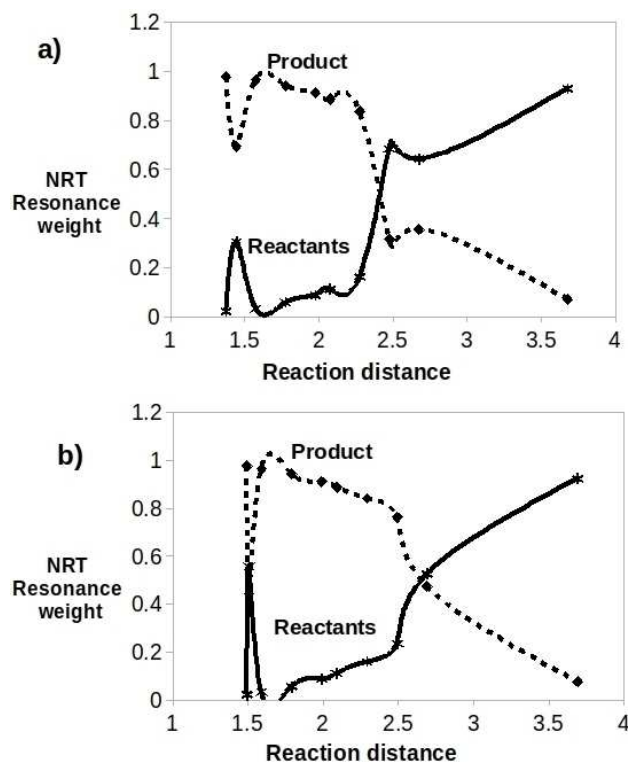


Figure 8. The NRT resonance weight of the reactants and product along the chosen reaction path for a) Lactam 3 and b) Lactam 4.

expected, the weight of the product decreases while the weight of the reactant increases as the distance along the reaction path increases. It is interesting to point out that the structure of transition state for lactam 4 (around 1.5 Å) have relatively equivalent weight for both product and reactants. However, lactam 3 have more product weight as compared to corresponding reactants. Hence, there is equal probability for the formation of lactam 4 as it can easily form product or falls back to reactants from the transition state. However, in solvent medium and at higher temperature there is more tendencies towards formation of the product because of the higher entropy of its reactants as shown in Figure 8.

The changes in some of the selected bonds are also studied along the reaction path to measure the change in their bond order as shown in Figure 9. Virtually all the selected bonds

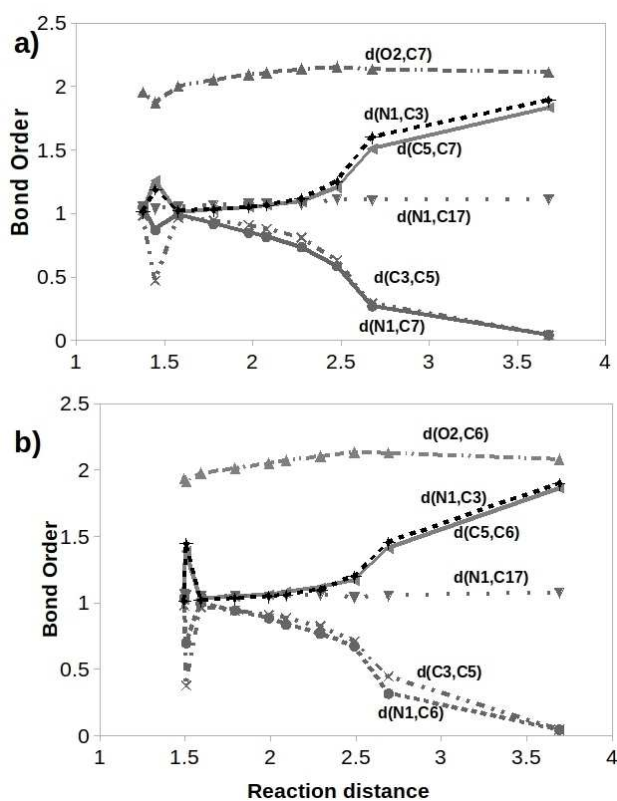


Figure 9. Changes in the bond order of selected bonds along the the reaction path for a) lactam 3 and b) lactam 4.

were significantly affected in the transition states of the two lactams 3&4 (around 1.5 Å). The bond order of the atoms that are involved in the plane of the reaction for lactam 3 (N₁-C₇, C₃-C₅) and lactam 4 (N₁-C₆, C₃-C₅) decrease significantly at the transition state while the bond order of the associated atoms in each of their fragment increase hence, indicating the bond breaking mechanism from product to reactants.

Atomic and Molecular Properties

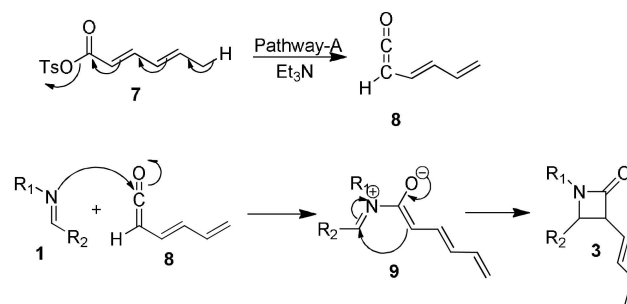
The imaginary frequency of the lactam 3 was observed at -127.19 with intensity of 141.26 having significant contribution from the benzene ring torsional angle of H34-C33-C35-C37 (24%, -180.62) while that of lactam 4 was observed at -169.10 with a lower intensity 77.38 having contribution from the benzene ring bending angle H34-C33-C35 (14%, 120.08°) and torsional angle H34-C33-C35-C37 (29%, -180.00).³¹

The resonance structure (RS) study of the lactam 3 & 4 and their transition state structures are tabulated in Table S1 in supporting information.^[31] These studies clearly predict the possible bond formation and bond breaking (in bracket) with the percentage possibilities as a measure of resonance weight. The product and the transition state of lactam 4 have higher resonance possibility of fragmentation along the N1-C6 bond while lactam 3 in the transition state have significant possibility of fragmented along the C3-C5 bond.

The atomic isotropic NMR shielding of the atoms of the lactam 3 and 4 in the close proximity of the reaction plane are shown in Table S2 and S3 with the contribution of the other electronic orbitals. The lactam 3 nitrogen atoms are strongly de-shielded by the fragment bonding (N1-C7) as compared to the lactam 4 (N1-C6) but to a lesser extent. In all the selected atoms, the associated bonds strongly de-shielded the isotropic shielding tensor of the atoms. A wider range of electronic effects is also noted in lactam 4 as the nitrogen atoms on fragment 2 play more shielding effects on the oxygen atom compare to lactam 3. This could be responsible for the higher charge transfer observed in lactam 4.

The natural energy decomposition analysis (NEDA) is also studied and results are tabulated in Table S4. There is relatively higher fragment interaction and stability of the lactam 4 (-746.95 kCal/mol) as compared to lactam 3 (-716.03 kCal/Mol). This is obviously because of stronger charge transfer within the fragments of lactam 4 as compared to lactam 3.

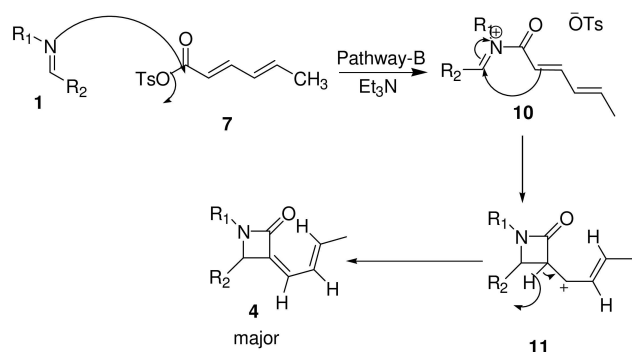
On the basis of experimental observations and theoretical calculations, a mechanism has been proposed. Both experimental observations as well as theoretical calculations have predicted the formation of 3-butadienyl-azetidin-2-ones 3 and 3-but-2-enylidene-azetidin-2-ones 4 is kinetically and thermodynamically controlled respectively. The reactions initially involves *in situ* formation of sorbyl tosylate by addition of TsCl in sorbic acid. The sorbyl tosylate may have undergone two different types of pathways (Pathway-A or Pathway-B) for the synthesis of two different lactams 3&4 as described in Scheme 1&2. The synthesis of 3-butadienyl-azetidin-2-ones 3



Scheme 1. Mechanism for the formation 3-butadienyl-azetidin-2-ones 3

follow **pathway-A**. It involve the formation of butadienyl ketene 8 at low temperature which reacts with imine to yield zwitterionic intermediate 9 followed by the ring closure to yield 3 as major product at low temperature (Scheme 1).

However at elevated temperature, the sorbic tosylate 7 directly reacts with iminic nitrogen via addition reactions to afford an zwitterionic intermediate 10 which collapsed to an another intermediate 11 by ring closure electrocyclizations. An abstraction of acidic ring proton by base leads to the formation of 3-but-2-enylidene-azetidin-2-ones 4 as major adduct at elevated temperature (Scheme 2).²¹⁻²³



Scheme 2. Mechanisms for formation of 3-but-2-enylidene-azetidin-2-ones 4.

The synthesized compounds were evaluated for their antimicrobial activity against the *E. coli*, *S. aureus*, *P. aeruginosa*, *B. cereus* and *B. subtilis* for their minimum inhibitory concentrations (MIC, $\mu\text{g/mL}$) and the results are provided in Table 4.

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>B. cereus</i>	<i>B. subtilis</i>
4a	250	125	125	125	250
4b	250	125	125	31.25	250
4c	250	125	250	250	250
4d	250	250	62.5	62.5	250
4e	250	125	125	24.8	250
4 h	250	125	125	250	250
6a	250	250	125	62.5	250
Sulfanilamide	125	125	62.5	62.5	62.5
Sulfamethoxazole	62.5	15.62	31.25	15.62	15.62
Ampicillin	31.25	62.5	0.48	0.48	7.81
DMSO	-	-	-	-	-

As evident from Table 4, the antimicrobial activity of the test compounds were found to be dependent upon the nature of substituent at N-1 position as well as the presence of nature of styryl group at C-4 position of lactam ring. The presence of a cyclohexyl group substituent at N-1 position of lactam ring of the synthesized exocyclic adducts considerably improved the activity profile as evident by compound 4e. Further, the introduction of different moieties remarkably improved the antimicrobial activity with a preference for Ph, *p*-CH₃-Ph and *p*-OCH₃-Ph at N-1 position of lactam ring by compounds 4a, 4b and 4d. Introduction of styryl group at C-4 position of lactam ring position enhance the activity profile as evident by compound 6a.

The α -alkylidene- β -lactams 4 were also explored in the synthesis of spiro- β -lactam 14 (Table 5). The α -alkylidene- β -lactams easily underwent [4 + 2] cycloaddition reactions with 4-methyl-[1,2,4]triazole-3,5-dione 13 to yield spiro[[1,2,4]triazolo

S.No.	Entry	R	Conditions	Yield (%) ^a
1.	14a	-H	THF, -78°C	69
2.	14b	-CH ₃	THF, -78°C	62
3.	14c	-OCH ₃	THF, -78°C	75

^aIsolated yield after purification.

[1,2-*a*]pyridazine-5,3'-azetidine]-1,2',3(2*H*,8*H*)-triones 14 as reported in literature.²³

Conclusions

In conclusion, we have explored the [2 + 2] cycloaddition reactions of sorbic tosylate at high temperature (80 °C) with variety of imines. These reactions entails a facile diastereoselective route for functionally decorated α -alkylidene- β -lactams. The developed protocol is not associated with the typical drawbacks linked with the conventional protocols. The theoretical calculations reveals that α -alkylidene- β -lactams 4 is thermodynamically more favorable product accounting for its sole formation at high temperature under experimental conditions. The synthesized scaffolds were evaluated for their antimicrobial activity against the *E. coli*, *S. aureus*, *P. aeruginosa*, *B. cereus* and *B. subtilis*. The synthesized α -alkylidene- β -lactams were also explored as functionalized dienes for the synthesis of spirocyclic lactams in good yields. The current study is an important in terms on mechanistic insight in to the reaction of butadienylketene/sorbic tosylate with imines and the usefulness of α -alkylidene- β -lactams as vital organic synthon as well as a diverse pharmacophore.

Supporting Information Summary

General procedure for the synthesis of 3-but-2-enylidene-1,4-diaryl-azetidin-2-one (4): To a well-stirred solution of imine 1 (10 mmol) with sorbic acid 2 and triethylamine (15 mmol) in dry 1,2-dichloroethane (30 ml) was added dropwise a solution of *p*-toluenesulphonylchloride in dry 1,2-dichloroethane (30 ml) over a period of 0.5 h at 80 °C temperature. After completion of the reaction (tlc), the reaction mixture was first washed with water and the organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated and solid residue was purified by flash column chromatography using silica gel (100: 200 mesh) in EtOAc:cyclohexane (1:9) as an eluent system to get pure compound 4.

Computational method

The optimization was done with hybrid DFT method M062X that is known to be good for thermodynamic and kinetic calculation^[24] and basis set 6–311G(d,p) using Gaussian 09 (G09).^[25] The associated properties with the natural bond orbital (NBO) analysis^[26] and natural energy decomposition analysis (NEDA)^[27] were obtained using NBO 6.0G program^[28] and FIREFLY 8.1.G^[29] which is partially based on the GAMESS (US)^[30] source code.

For full experimental details, see Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: α -alkylidene- β -lactam · azadiene · butadienylketene · β -lactam · spirocycles

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