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SYNTHETIC STUDIES ON THE ROLE OF SUBSTITUENTS AT C-3 POSITION ON C3-C4 BOND CLEAVAGE OF *β*-LACTAM RING: CONVENIENT ROUTE FOR DIASTEREOSELECTIVE SYNTHESIS OF PYRIDIN-2-ONES

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Abstract — The manuscript explicates the detailed synthetic studies on the effect of substituents at C-3 position of 2-azetidinones on the selective C-3/C-4 cleavage resulting in the diastereoselective synthesis of 2-pyridones further corroborated by computational studies. The manuscript assumes significance as the developed protocol does not suffer from the drawbacks associated with conventional methodologies *viz.* multistep and harsh conditions along with poor regio- and chemo selectivity and thus can be easily manipulated for the synthesis of multi-functionalized pyridine-2-ones.

INTRODUCTION

The pyridin-2-one ring represents an important structural motif occurring in many natural products and related congeners and has attracted the attention of synthetic organic chemists for many years as it exhibits a wide range of biological activities.[1] For example, cytisine, extracted from the seeds of *Laburnum anagyroides* acts as a partial agonist of nicotinic cholinergic receptors (nAChRs) with a nanomolar affinity and a high selectivity for the $\alpha_4\beta_2$ subtype;[2] Farinosone, isolated from the entomopathogenic fungi *Paecilomyces farinosus* and *Paecilomyces militaris* induces and enhances neurite outgrowth in the PC-12 cell line;[3] apiosporamide, isolated from the fungus *Apiospora montagnei Saccardo* exhibits potent antifungal activity against the coprophilous fungus *Ascobolus furfuraceus* and

Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

shows antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*.[4] Amrinone, milrinone and their analogues which have 2-pyridone moiety are used as cardiotonic agents for the treatment of heart failure.[5] 2-Pyridone derivatives are also a versatile synthon for the preparation of a variety of other nitrogen-containing heterocycles, such as *β*-lactam, quinolizidine, pyridine, piperidine, and indolizidine alkaloids;[6] and have also been used as lead compounds for the synthesis of selective anticancer,[7] antiviral[8] as well as inhibitors of Aβ-peptide aggregation drugs which play an important role in amyloid formation in Alzheimer's disease.[9]

Amino-2-pyridones are an important subsets of 2-pyridones; exhibiting a wide range of interesting biological activities,[10] which include as interleukin-2 inducible T-cell (Itk) inhibition,[10a] glycogen synthase-3b inhibition,[10b] insulin-like growth factor-1 receptor (IGF- 1R) inhibition,[10c] EP3 receptor antagonism,[10d] and selective tissue Factor VIIa inhibition,[10e] among other medicinal properties.[10f,g] The recently developed protocols for the preparation of aminopyridones involve the reactions such as that of amine with *α*-dicarbonylallene,[11a] acyclic ketene aminals with propiolic acid ester[11b] and ring closing metathesis of *α*-aminoacrylamide,[12] apart from the conventional methodologies involving reduction of nitropyridones[13] or amination of halopyridones.[14] Although these protocols provide access to variedly functionalized aminopyridones, they invariably suffer from significant limitations *viz.* multistep procedure, harsh conditions, low yields along with the poor chemo- and regioselectivity.

β-Lactams, in addition to their biological profile as inhibitors of serine enzymes of mammalian, bacterial, and viral origin,[15] have also been widely recognized as synthetic building blocks due to the possible ring cleavage at any of the four single bonds of the lactam ring. The most common cleavage of the amide bond is the basis of biological action of *β*-lactam group of antibiotics[16] as well as the recently developed inhibitors of human leukocyte elastase[17] and human cytomegalovirus protease.[18] However, there are very few reports regarding the C(3)-C(4) bond cleavage of *β*-lactam nucleus involving either the Cope rearrangement.[19]

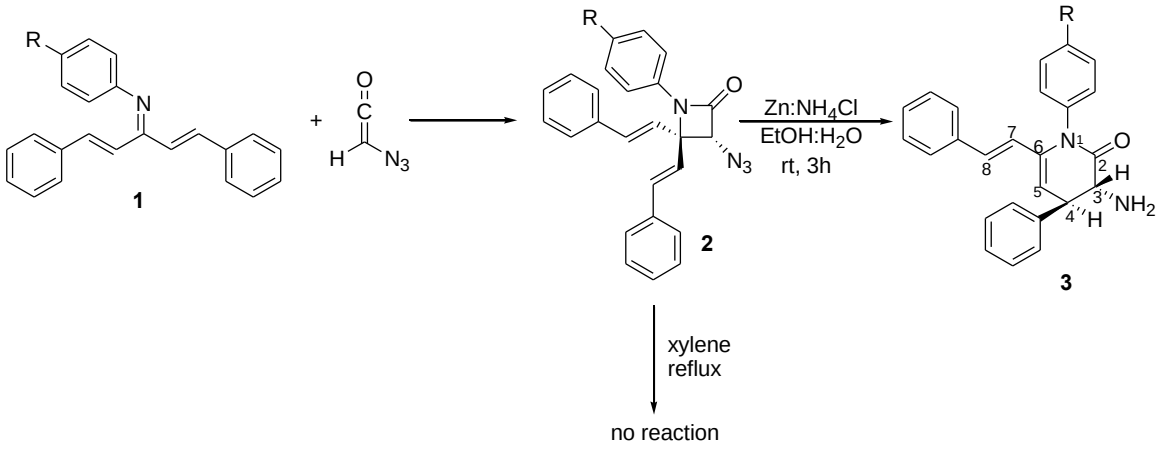
In continuation of our pursuits for the synthesis of novel heterocyclic compounds of medicinal potential,[20] and our recent exposure to the prospective of *β*-lactam synthon approach for the synthesis of novel heterocyclic compounds,[21] the present manuscript describes the diastereoselective synthesis of pyridones *via* the much less explored C3-C4 cleavage of *β*-lactam ring influenced by the electronic nature of substituents at C-3 position.

RESULTS AND DISCUSSION

SYNTHETIC CHEMISTRY

The beginning of our synthetic endeavour involved an initial Staudinger reaction of appropriately substituted imine **1** with azidoketene generated *in situ* from azido acetic acid and *p*-toluenesulfonyl

chloride in the presence of triethylamine **(Scheme-1)**. The reaction led to the formation of desired 3-azido-2-azetidinones **2** characterized on the basis of spectral data and analytical evidences. The azetidinones **2** were then examined for further synthetic transformations *viz.* refluxing in xylene, reduction to corresponding amine as well as Staudinger reaction with triphenylphosphine. The azetidinones **2** on refluxing failed to produce any significant transformation while the reduction using Zn/NH_4Cl protocol[22] resulted in the isolation of corresponding pyridones **3 (Scheme-1)** in good yields as shown in **Table 1**.



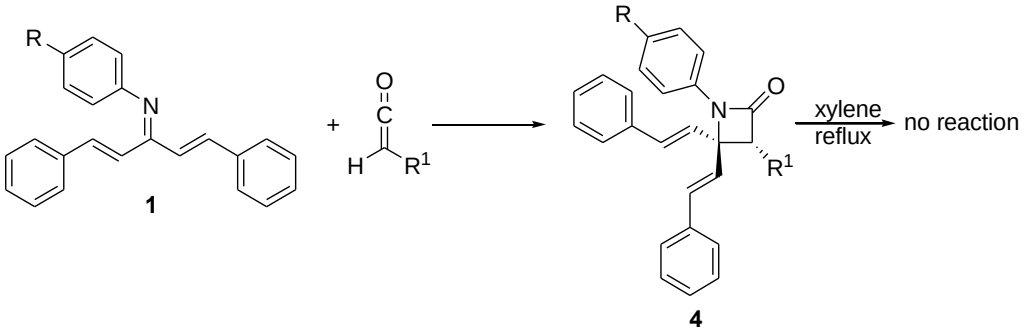
Scheme 1

The synthesized diastereoselective 2-pyridones **3** have been assigned structure on the basis of spectral and analytical evidences. The IR spectrum of compound **3a**, for example showed the sharp absorption peak at 1680 cm^{-1} instead of a peak at 1756 cm^{-1} corresponding to the carbonyl of lactam ring. The salient features of its ^1H NMR include a doublet at δ 3.78 (J = 12.6 Hz) corresponding to H^3, a doublet of a doublet at δ 3.91 (J = 12.6 Hz, 7.2 Hz) corresponding to H^4 and a doublet at δ 5.68 (J = 7.2 Hz) corresponding to H^5. The coupling constant of 12.6 Hz confirms the *trans* stereochemical relationship between H^3 and H^4.

Table 1. Transformation of 3-azido-2azetidinones to 3-amino-2-pyridones

Entry	Azatriene	R	Product	Yield (%)	Reaction Conditions	Product	yield (%)
1	**1a**	H	**2a**	80	Zn/NH_4Cl,MeOH/H_2O	**3a**	90
2	**1b**	Me	**2b**	82	Zn/NH_4Cl,MeOH/H_2O	**3b**	92
3	**1c**	Cl	**2c**	80	Zn/NH_4Cl,MeOH/H_2O	**3c**	94
4	**1d**	F	**2d**	84	Zn/NH_4Cl,MeOH/H_2O	**3d**	95

In order generalize the above observations and rationalize the electronic effect of substituents at C-3 position of the *β*-lactam ring on C-3/C-4 cleavage a range of 3-functionalized 2-azetidinones having electron withdrawing (phthalimido, chloro, 4-nitrophenyl) substituents at C-3 position have been synthesized in good yields **(Table 2)**. The synthesized 2-azetidinones **4** failed to undergo any significant transformation even under stringent reaction conditions *viz.* refluxing in xylene for 48 hrs **(Scheme-2)**.

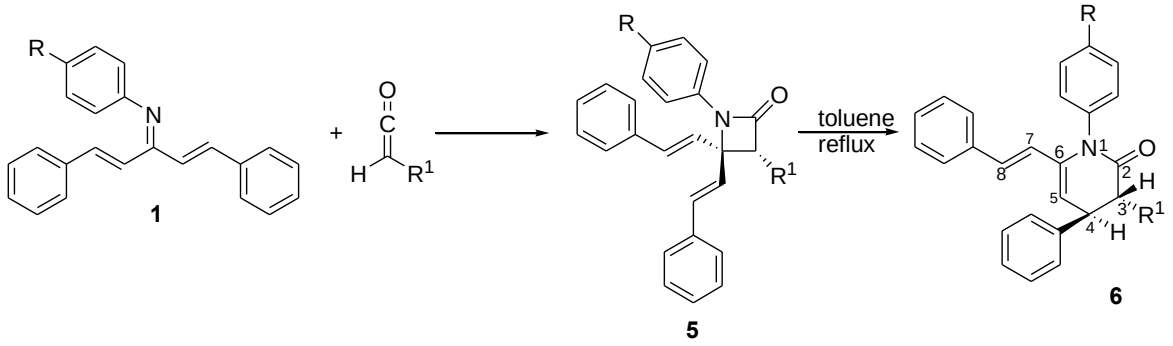


Scheme 2

Table 2. Effect of substituents at C-3 position on C(3)-C(4) cleavage of *β*-lactam ring

Entry	Azatriene	R	R^1	Product	Yield(%)	Reaction Conditions	Product	Yield(%)
1	**1a**	H	Cl	**4a**	82	xylene reflux, 48h	no reaction	--
2	**1b**	Me	Cl	**4b**	80	xylene reflux, 48h	no reaction	--
3	**1c**	Cl	Cl	**4c**	84	xylene reflux, 48h	no reaction	--
4	**1d**	F	Cl	**4d**	82	xylene reflux, 48h	no reaction	--
5	**1a**	H	phthalamido	**4e**	86	xylene reflux, 48h	no reaction	--
6	**1b**	Me	phthalamido	**4f**	85	xylene reflux, 48h	no reaction	--
7	**1c**	Cl	phthalamido	**4g**	84	xylene reflux, 48h	no reaction	--
8	**1d**	F	phthalamido	**4h**	81	xylene reflux, 48h	no reaction	--
9	**1a**	H	*p*-NO_2-C_6H_4	**4i**	85	xylene reflux, 48h	no reaction	--
10	**1b**	Me	*p*-NO_2-C_6H_4	**4j**	80	xylene reflux, 48h	no reaction	--
11	**1c**	Cl	*p*-NO_2-C_6H_4	**4k**	82	xylene reflux, 48h	no reaction	--
12	**1d**	F	*p*-NO_2-C_6H_4	**4l**	83	xylene reflux, 48h	no reaction	--
13	**1a**	H	-SMe	**5a**	86	toluene reflux, 8h	**6a**	95
14	**1b**	Me	-SMe	**5b**	84	toluene reflux, 8h	**6b**	94
15	**1c**	Cl	-SMe	**5c**	83	toluene reflux, 8h	**6c**	93
16	**1d**	F	-SMe	**5d**	80	toluene reflux, 8h	**6d**	95
17	**1a**	H	-OMe	**5e**	82	toluene reflux, 8h	**6e**	92
18	**1b**	Me	-OMe	**5f**	85	toluene reflux, 8h	**6f**	94
19	**1c**	Cl	-OMe	**5g**	83	toluene reflux, 8h	**6g**	93
20	**1d**	F	-OMe	**5h**	80	toluene reflux, 8h	**6h**	90

Further, polar donating groups *viz.* thiomethyl and methoxy have been introduced at C-3 position of 2-azetidinones *via.* [2+2] cycloaddition reactions of funtionalized imines with substituted ketenes as shown in **Scheme 3**. The synthesized 2-azetidinones **5** on refluxing in toluene interestingly resulted in the isolation of corresponding pyridones **6**, thus authenticating our observation that the presence of a polar donating group at C-3 promotes [1,3] shift preceded by C-3/C-4 bond cleavage.



Scheme 3

COMPUTATIONAL RESULTS

The effect of electron donating and electron withdrawing groups on C2-C3 bond cleavage, observed under experimental conditions, was supported by two molecular dynamics (MD) simulations performed on the β-lactams **2a** and **4a** bearing $–NH_2$ and –Cl substituent, respectively at position C-3. In order to mimic the reaction conditions, **2a** and **4a** were solvated with methanol **(Figure 1)** and toluene (not shown) solvent molecules, respectively.

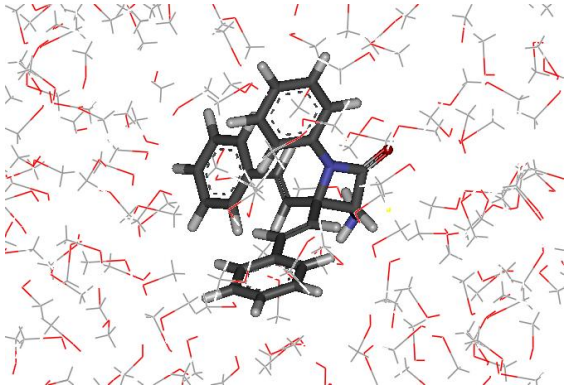


Figure 1. The lactam **2a** soaked in a box of methanol molecules. The ligand is represented in sticks form while the methanol molecules are shown in lines.

The MD simulations of length 1 nanosecond (1ns) were performed at molecular mechanics level using the AMBER program,[23] and consequently 1000 conformations of each lactam were sampled. The structural details of initial structures and ten sampled conformations of each lactam are summarized in **Tables 3-4**. A closer inspection of **Table 3** indicated a significant variation in the bond length (C2-C3) of sampled conformations ranging between 1.59 Å to 1.68 Å, clearly suggesting a considerable flexibility of this bond in **2a**.

Table 3. Structural parameters of initial and ten sampled conformations of **2a** obtained from the MD

Conformer Number	Bond	Bond length status C2-C3(Å)	Dihedral C19-C3-C2-C8	Dihedral C3-C2-C8=C10	Dihedral C19-C3-C2-C8	Dihedral C3-C2-C7=C12
Starting	1.59	stable	132.5	-146.4	-1.5	-86.4
1	1.58	stable	118	117.6	-5.8	-83.7
2	1.55	stable	123.4	81.9	8.4	-87.0
3	1.59	stable	129.5	105.3	6.9	-85.0
4	1.57	stable	128.2	126.7	5.1	-72.5
5	1.60	stable	119	114.6	-5.6	-86.7
6	1.55	stable	124.4	91.9	6.4	-87.0
7	1.58	stable	125.5	102.3	7.9	-88.0
8	1.55	stable	130.2	127.7	7.1	-73.5
725	1.62	stable	122.8	71.9	-4.5	-142.0
779	1.63	unstable	123.5	66.4	5.92	-109.7

Table 4. Structural parameters of initial and ten sampled conformations of **5a** obtained from the MD

Conformer Number	Bond	Bond length status C2-C3	Dihedral N8-C3-C2-C7	Dihedral C3-C2-C7=C14	Dihedral N8-C3-C2-C15	Dihedral C3-C2-C15=C16
Starting	1.59	stable	5.4	-80.7	138.4	-152.4
1	1.61	stable	-7.3	88.0	126.3	-170.9
2	1.68	unstable	-14.7	90.5	122.0	175.7
3	1.67	unstable	-17.7	85.6	119.5	-173.2
4	1.64	unstable	-7.4	78.4	122.0	-167.5
5	1.61	stable	-4.1	82.5	130.5	-163.1
6	1.63	unstable	-12.8	92.4	119.8	174.2
7	1.68	unstable	-19.9	79.11	116.1	177.9
8	1.60	stable	-15.9	91.1	116.9	-179.3
9	1.56	stable	-14.7	95.7	118.7	-160.4

The visual inspection of conformations revealed the breakage of C2-C3 bond when bond length is >1.62 Å, as depicted for conformation (number **4)** of **2a** in **Figure 2a**. The average fluctuation of C2-C3 around 1.63 Å for 1000 conformations **(Figure 2b)** further indicated a consistent unstable nature of this bond in the whole MD trajectory of lactam **2a**.

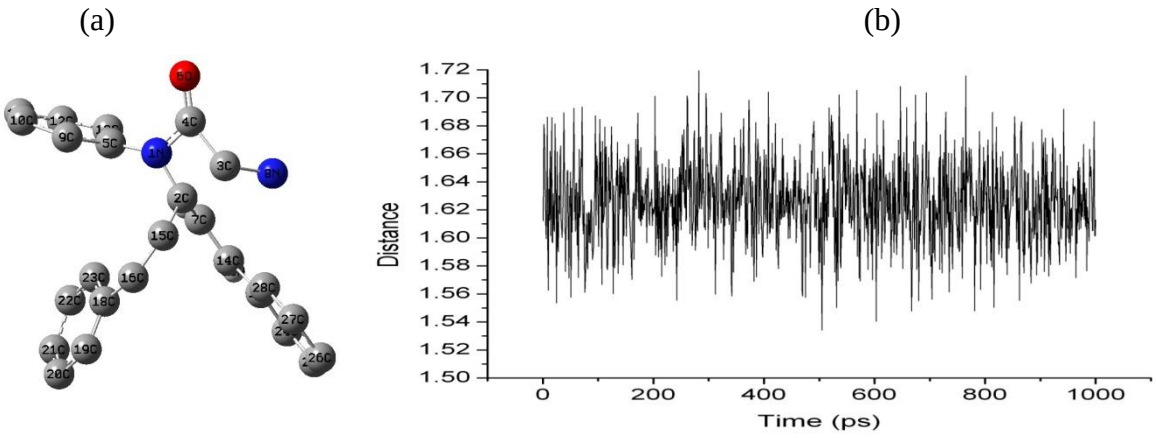


Figure 2. Conformation number 4 (Table 1) without solvent molecules **(a**), and the evolution of C2-C3 bond distance during the progress of MD trajectory in lactam **2a (b)**.

The average bond length (C2-C3), however, was quite stable in case of lactam **4a** (Conformer **5**, **Figure 2a**) fluctuating around ~ 1.60 Å **(Figure 3b)** in approximately 95% conformations of the MD trajectory. It is assumed that the presence of $–NH_2$ group at position C-3 lowers the strength of C2-C3 bond probably *via* its +I (Induction) effect through the intervening electrons of bonded atoms. The –Cl group (electron withdrawing group) present at C-3 position, on other hand, stabilizes and increases the C2-C3 bond strength *via* its –I effect.

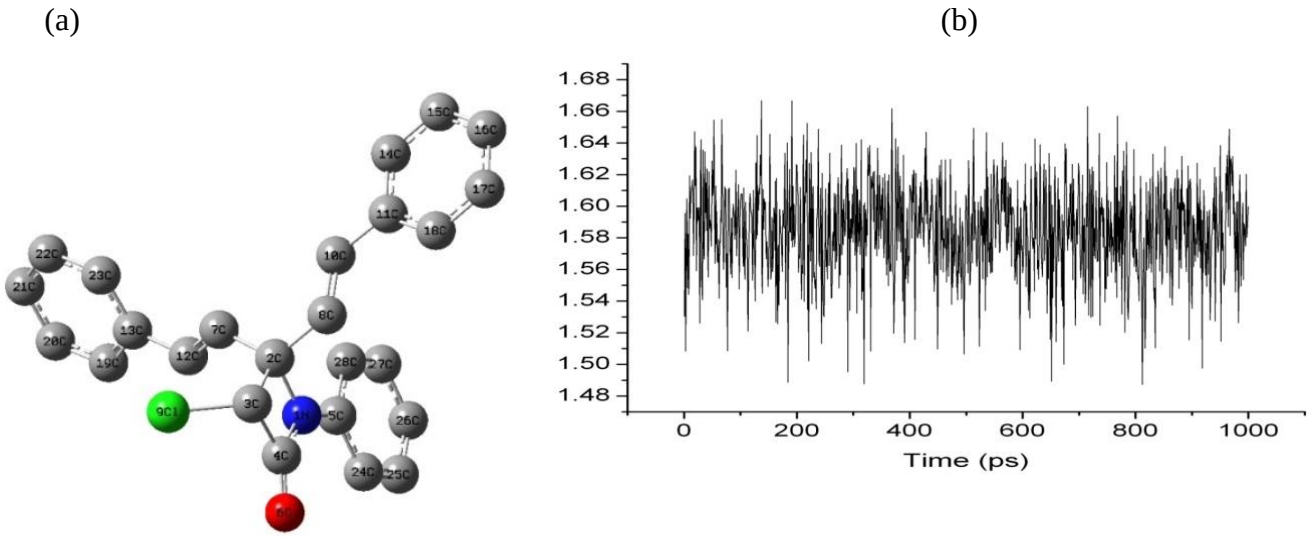


Figure 3. Conformation number 5 **(Table 4)** without solvent molecules **(a**), and the evolution of C2-C3 bond distance during the progress of MD trajectory in lactam **2a (b)**

Figures 4a-d represents the evolution of dihedral angles during the progress of MD simulations in both *β*-lactams. The average fluctuation of computed dihedral angles around -13 (N8-C3-C2-C7) and 102 (C3-C2-C7=C14) for **2a (Figures 4a-b)**, and ~130 (Cl9-C3-C2-C8) and ~118 (C3-C2-C8=C10) for **4a (Figure 4c-d)**, suggested a better overlapping plane for the electronic induction (EI) in former than the later. The corresponding dihedral angles for second styryl functionality in both **2a** (N8-C3-C2-C15 and C3-C2-C15=C16) and **4a** (Cl9-C3-C2-C7 and C3-C2-C7=C12) were in an unfavourable plane **(Figures 2a, 3a)** clearly ruling out its possible involvement in EI. It should be noted that the suitability of the dihedral planes for efficient EI was only based on the visual inspection of 3D structures showing intact C2-C3 bond, as it would be imprecise to compute them in the absence of it due to fast conformational changes in the structures.

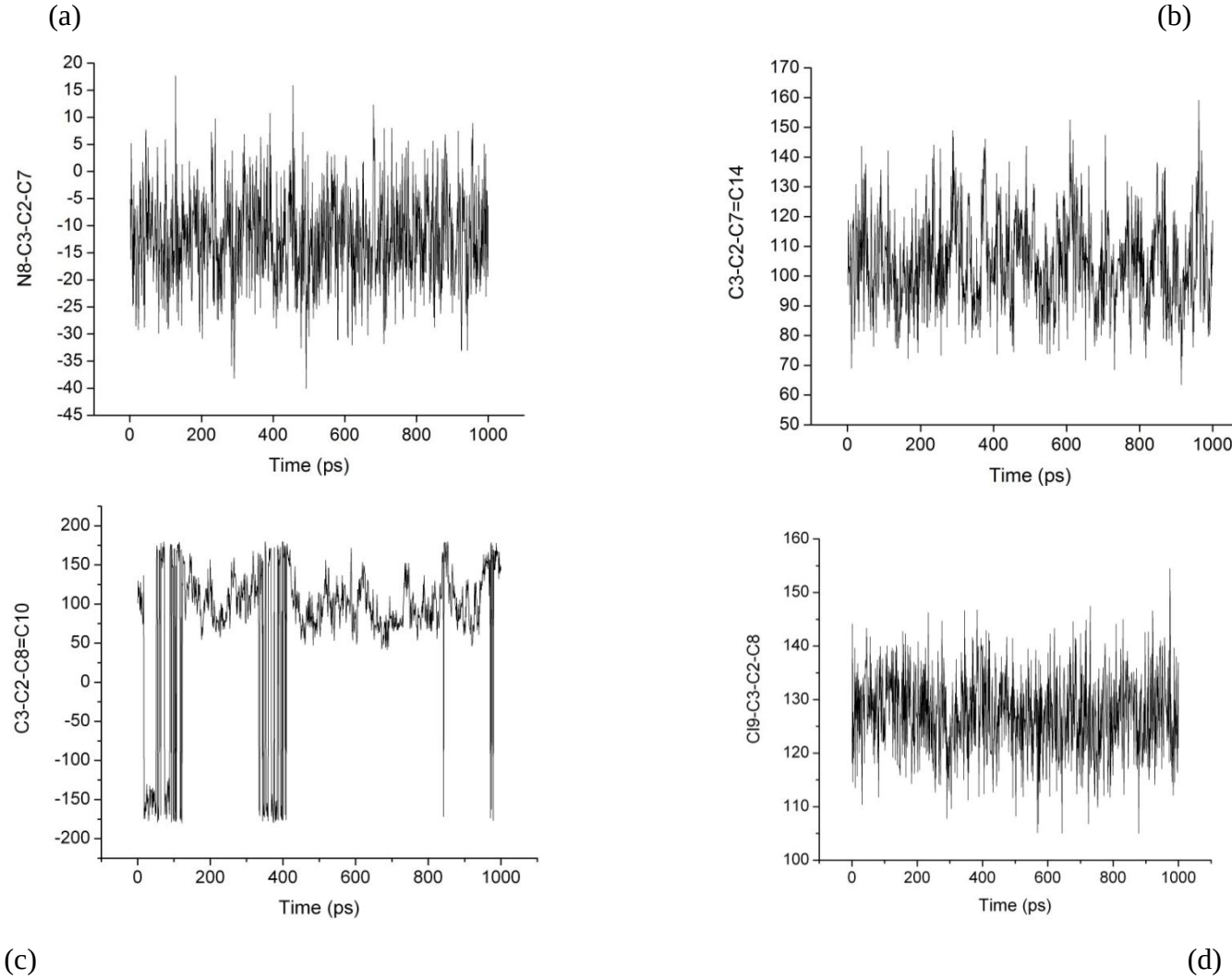
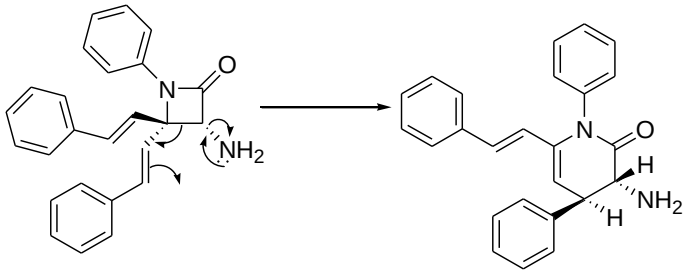


Figure 4. The progress of dihedrals N8-C3-C2-C7 and C3-C2-C7=C14 in lactam **2a**, and Cl9-C3-C2-C8 and C3-C2-C8=C10 in lactam **4a**, during the progress of MD trajectories.

Overall, the MD results indicate that the conversion of lactams into pyridones, observed in present study, proceeds probably *via* two steps. The first step involves the breakage of C2-C3 bond, and is significantly affected by the electronic nature of the substituents (electron donating/withdrawing) attached to the C-3 atom of C2-C3 bond, and could be a rate determining step for the reaction. In second step, the rapid conformational changes takes place in the intermediate formed after C2-C3 bond cleavage, and leads to the formation of six-membered pyridones probably *via* facile ring cyclization of the intermediate as depicted in **Scheme 4**.



Scheme 4

CONCLUSION

In conclusion, a convenient route for the diastereoselective synthesis of functionalized 2-pyridones has been developed *via* C-3/C-4 bond cleavage of 2-azetidinones. The effect of various electron withdrawing as well as electron donating substituents on the C-3/C-4 bond cleavage has been studied. Interestingly the presence of polar donating substituents at C-3 position of the synthesized 2-azetidinones facilitate 1,3 sigmatropic shift proceeding C-3/C-4 bond cleavage. The synthetic observations have been further corroborated by computational studies. The manuscript further assumes significance as the developed protocol does not suffer from the drawbacks associated with conventional methodologies *viz.* multistep and harsh conditions along with poor regio- and chemo selectivity and thus can be easily manipulated for the synthesis of multi-functionalized pyridine-2-ones.

EXPERIMENTAL

Computational Methodology

Molecular dynamics (MD) simulations were performed within the framework of molecular mechanics using the Amber 9.0 program.[23] The 3D structures of lactams **2a** and **4a** were geometrically optimized using Forcite module in Material Studio (MS).[24] The Restrained Electrostatic Potential (RESP) atomic charges consistent with the Amber program were computed for both structures using the General Amber Force Field (GAFF) in AMBER. The lactams **2a** and **4a**, prior to simulations, were soaked in solvent boxes with dimensions of 34.4 x 35.4 x 35.8 Å and 29.2 x 33.1 x 34.2 Å for methanol and toluene, respectively. Both systems were then energetically minimized using 5,000 steps of steepest descent, followed by conjugate gradient until their energies were lower than 0.001 kcal mol^{-1}Å. Thereafter, the whole system of **2a** and **4a** were equilibrated for 500 ps at temperature of 300K and 385K, respectively, using the periodic boundary conditions (PBC). The production run of each MD involved 1ns (1000 ps) and each snapshot was sampled at the interval of 1 ps. The PTRAJ module of AMBER 9.0 was used for the analysis of both MD trajectories.

Chemistry

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Jeol 300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on Jeol 300 (75 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120 mesh). All the starting materials as well as the products were racemates.

General methods for the preparation of compound (2a-d):

A solution of *p*-toluenesulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), azidoacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was further purified by column chromatography on silica gel by using 5% EtOAc/hexane as eluent.

2a. 3-Azido-1-phenyl-4,4-distyrylazetidin-2-one

Yellow oil. IR (KBr): 2100, 1756, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 1H, H-lactam ring), 6.48 (d, *J* = 16.5 Hz, 1H, α-H (styryl)), 6.72 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.91 (d, *J* = 16.5 Hz, 1H, α-H (styryl)), 7.22–7.48 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.4, 63.6, 120.3, 123.2, 124.2, 126.3, 127.2, 127.6, 128.3, 128.8, 134.9, 140.7. MS *m/z* 393 $(M)^+$. Anal. Calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28. Found: C, 76.48; H, 5.07; N, 14.22.

2b. 3-Azido-4,4-distyryl-1-*p*-tolylazetidin-2-one

Yellow oil. IR (KBr): 2108, 1752, 1528 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.28 (s, 3H, -CH_3), 4.60 (s, 1H, H-lactam ring), 6.47 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 6.71 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.90 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 7.21–7.47 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 20.9, 57.3, 63.4, 120.2, 123.3, 124.4, 126.4, 127.3, 127.8, 128.2, 128.7, 134.8, 140.7, 170.2. MS *m/z* 407 $(M)^+$. Anal. Calcd for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.79; H, 5.41; N, 13.71.

2c. 3-Azido-1-(4-chlorophenyl)-4,4-distyrylazetidin-2-one

Yellow oil. IR (KBr): 2107, 1748, 1530 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 4.62 (s, 1H, H-lactam ring), 6.46 (d, *J* = 16.5 Hz, 1H, α-H (styryl)), 6.70 (d, *J* = 16.5 Hz, 2H, *β*-H (styryl)), 6.91 (d, *J* = 16.5 Hz, 1H, α-H (styryl)), 7.20–7.48 (m, 14H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 57.4, 63.6, 120.3, 123.4, 124.5, 126.6, 127.1, 127.7, 128.3, 128.8, 134.7, 140.6, 170.3. MS *m/z* 427 $(M)^+$. Anal. Calcd for $C_{25}H_{19}ClN_4O$: C, 70.34; H, 4.49; N, 13.12. Found: C, 70.30; H, 4.43; N, 13.08.

2d. 3-Azido-1-(4-fluorophenyl)-4,4-distyrylazetidin-2-one

Yellow oil. IR (KBr): 2100, 1735, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 4.60 (s, 1H, H-lactam ring), 6.43 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.71 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.89 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.19–7.46 (m, 14H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 57.5, 63.4, 120.2, 123.5, 124.7, 126.5, 127.2, 127.8, 128.2, 128.7, 134.6, 140.5, 170.5. MS *m/z* 427 $(M)^+$. Anal. Calcd for $C_{25}H_{19}FN_4O$: C, 73.16; H, 4.67; N, 13.65. Found: C, 73.11; H, 4.62; N, 13.59.

General methods for the preparation of Compound (3a-d):

To a well stirred solution of 3-azido-2-azetdinone **2** (1 mmol) in mixture of EtOH or MeOH: water (80:20) was added NH_4Cl (2.5 mmol) and zinc powder (2.5 mmol). The reaction mixture was allowed to stir at room temperature till the completion of reaction as evidenced by TLC**.** Liquid ammonia was added to alkaline the reaction mixture. Water and EtOAc was added to the reaction mixture and organic layer was extracted. Organic layer was washed 5-6 times with brine solution, separated and dried over anhydrous Na_2SO_4. The evaporation of solvent under reduced pressure yield the pure product.

3a. 3-Amino-1,4-diphenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 107-109 ^oC. IR (KBr): 1682, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 3.78 (d, *J* = 12.6 Hz, 1H, H^3), 3.91 (dd, *J* = 12.6 Hz, 7.2 Hz, 1H, H^4), 4.75 (s, 2H, -NH_2, exchangeable with D_2O), 5.68 (d, *J* = 7.2 Hz, 1H, H^5), 6.10 (d, *J* = 15.9 Hz, 1H, H^7), 6.67 (d, *J* = 15.9 Hz, 1H, H^8), 7.09–7.41 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.5, 56.7, 110.7, 122.9, 126.5, 127.4, 127.9, 128.0, 128.1, 128.5, 128.9, 129.7, 130.8, 135.5, 136.3, 137.5, 139.2, 141.5, 171.6. MS *m/z* 367 $(M)^+$. Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found: C, 81.89; H, 6.01; N, 7.59.

3b. 3-Amino-4-phenyl-6-styryl-1-*p*-tolyl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 112-114 ^oC. IR (KBr): 1680, 1526 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.27 (s, 3H, -CH_3), 3.76 (d, *J* = 12.4 Hz, 1H, H^3), 3.92 (d, *J* = 12.4 Hz, 7.1 Hz, 1H, H^4), 4.75 (s, 2H, -NH_2, exchangeable with D_2O), 5.66 (d, *J* = 7.1 Hz, 1H, H^5), 6.11 (d, *J* = 15.9 Hz, 1H, H^7), 6.66 (d, *J* = 15.9 Hz, 1H, H^8), 7.10–7.45 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.9, 46.4, 56.6, 110.8, 122.7, 126.6, 127.3, 127.8, 128.0, 128.2, 128.5, 128.9, 129.6, 130.7, 135.4, 136.5, 137.6, 139.3, 141.6, 171.5. MS *m/z* 381 $(M)^+$. Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.01; H, 6.31; N, 7.32.

3c. 3-Amino-1-(4-chlorophenyl)-4-phenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. mp 110-112 ^{o}C. IR (KBr): 1678, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.77 (d, J = 12.5 Hz, 1H, H^3), 3.90 (d, J = 12.5 Hz, 7.2 Hz, 1H, H^4), 4.74 (s, 2H, -NH_2, exchangeable with D_2O), 5.65 (d, J = 7.2 Hz, 1H, H^5), 6.12 (d, J = 15.9 Hz, 1H, H^7), 6.65 (d, J = 15.9 Hz, 1H, H^8), 7.08–7.43 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.5, 56.7, 110.6, 122.8, 126.5, 127.4, 127.7, 128.1, 128.3, 128.6, 129.0, 129.5, 130.8, 135.5, 136.4, 137.7, 139.2, 141.7, 171.8; MS *m/z* 401 $(M)^+$. Anal. Calcd for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 8.84. Found: C, 74.86; H, 5.21; N, 8.80.

3d. 3-Amino-1-(4-fluorophenyl)-4-phenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 115-117 ^{o}C; IR (KBr): 1677, 1532 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.75 (d, J = 12.6 Hz, 1H, H^3), 3.93 (d, J = 12.6 Hz, 7.0Hz, 1H, H^4), 4.72 (s, 2H, -NH_2, exchangeable with D_2O), 5.67 (d, J = 7.0 Hz, H^5), 6.10 (d, J = 15.9 Hz, 1H, H^7), 6.64 (d, J = 15.9 Hz, 1H, H^8), 7.07–7.44 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.6, 56.5, 110.7, 122.7, 126.4, 127.3, 127.6, 128.1, 128.3, 128.7, 129.0, 129.4, 130.7, 135.4, 136.4, 137.6, 139.1, 141.5, 171.6; MS *m/z* 385 $(M)^+$. Anal. Calcd for $C_{25}H_{21}FN_2O$: C, 78.10; H, 5.51; N, 7.29. Found: C, 78.06; H, 5.47; N, 7.24.

General methods for the preparation of Compound (4a-d):

A solution of *p*-toluenesulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), chloroacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was further purified by column chromatography on silica gel by using 5% EtOAc/hexane as eluent.

4a. 3-Chloro-1-phenyl-4,4-distyrylazetidin-2-one

White solid. Mp 167-169 ^{o}C. IR (KBr): 1756, 1530 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.94 (s, 1H, H-lactam ring), 6.51 (d, J = 15.9 Hz, 1H, α-H (styryl)), 6.63 (d, J = 16.2 Hz, 2H, *β*-H (styryl)), 6.76 (d, J = 15.9 Hz, 1H, α-H (styryl)), 7.24–7.49 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 56.7, 63.7, 120.4, 123.3, 124.5, 126.4, 127.3, 127.7, 128.2, 128.7, 134.8, 140.6, 170.6; MS *m/z* 386 $(M)^+$. Anal. Calcd for $C_{25}H_{20}ClNO$: C, 77.81; H, 5.22; N, 3.63. Found: C, 77.75; H, 5.18; N, 3.58.

4b. 3-Chloro-4,4-distyryl-1-*p*-tolylazetidin-2-one

White solid. Mp 172-174 ^{o}C. IR (KBr): 1752, 1532 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.93 (s, 1H, H-lactam ring), 6.50 (d, J = 15.9 Hz, 1H, α-H (styryl)), 6.62 (d, J = 16.2 Hz, 2H, *β*-H (styryl)), 6.77 (d, J = 15.9 Hz, 1H, α-H (styryl)), 7.09 (d, J = 9.9 Hz, 2H, Ar-H), 7.22–7.47 (m, 12H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 56.6, 63.6, 120.3, 123.2, 124.4, 126.5, 127.2, 127.8, 128.3, 128.8, 134.9, 140.7, 170.3;

MS *m/z* 400.5 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNO$: C, 78.09; H, 5.54; N, 3.50. Found: C, 78.02; H, 5.47; N, 3.46.

4c. 3-Chloro-1-(4-chlorophenyl)-4,4-distyrylazetidin-2-one

White solid. Mp. 163-165 ^oC. IR (KBr): 1742, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, $-CH_3$), 4.91 (s, 1H, H-lactam ring), 6.51 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.63 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.78 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.08 (d, *J* = 9.9 Hz, 2H, Ar-H), 7.23–7.49 (m, 12H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 56.5, 63.4, 120.4, 123.3, 124.5, 126.6, 127.3, 127.7, 128.2, 128.7, 134.8, 140.6, 170.5; MS *m/z* 421 $(M)^+$. Anal. Calcd for $C_{25}H_{19}Cl_2NO$: C, 71.44; H, 4.56; N, 3.33. Found: C, 71.40; H, 4.49; N, 3.29.

4d. 3-Chloro-1-(4-fluorophenyl)-4,4-distyrylazetidin-2-one

White solid. Mp 178-180 ^oC. IR (KBr): 1738, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 4.90 (s, 1H, H-lactam ring), 6.49 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.62 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.77 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.07 (d, *J* = 9.9 Hz, 2H, Ar-H), 7.22–7.47 (m, 12H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C: 56.6, 63.3, 120.5, 123.4, 124.6, 126.7, 127.4, 127.8, 128.1, 128.8, 134.7, 140.5, 170.4; MS *m/z* 404 $(M)^+$. Anal. Calcd for $C_{25}H_{19}Cl_2FNO$: C, 74.35; H, 4.74; N, 3.47. Found: C, 74.31; H, 4.69; N, 3.41.

General methods for the preparation of Compound (4e-h):

A solution of *p*-toluenesulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), phthalamidoacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was further purified by column chromatography on silica gel by using 5% EtOAc/hexane as eluent.

4e. 2-(4-Oxo-1-phenyl-2,2-distyrylazetidin-3-yl)-isoindole-1,3-dione

White solid. Mp 140-142 ^oC. IR (KBr): 1748, 1526 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 5.48 (s, 1H, H-lactam ring), 6.48 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 6.61 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.74 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 7.12–7.85 (m, 19H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 59.5, 64.8, 119.9, 122.7, 123.8, 125.7, 126.5, 127.3, 127.7, 128.0, 128.8, 132.0, 133.5, 134.7, 140.6, 165.7, 170.6. MS *m/z* 497 $(M)^+$. Anal. Calcd for $C_{33}H_{24}N_2O_3$: C, 79.82; H, 4.87; N, 5.64. Found: C, 79.78; H, 4.81; N, 5.59.

4f. 2-(4-Oxo-2,2-distyryl-1-*p*-tolylazetidin-3-yl)-isoindole-1,3-dione

White solid. mp 147-149 °C. IR (KBr): 1735, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.27 (s, 3H, $-CH_3$), 5.47 (s, 1H, H-lactam ring), 6.49 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.63 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.73 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.10–7.86 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.7, 59.4, 64.7, 119.8, 122.6, 123.9, 125.5, 126.7, 127.2, 127.8, 128.2, 128.6, 132.1, 133.4, 134.8, 140.5, 165.7, 170.7; MS *m/z* 511 $(M)^+$. Anal. Calcd for $C_{34}H_{26}N_2O_3$: C, 79.98; H, 5.13; N, 5.49. Found: C, 79.91; H, 5.09; N, 5.43.

4g. 2-[1-(4-Chlorophenyl)-4-oxo-2,2-distyrylazetidin-3-yl]isoindole-1,3-dione

White solid. Mp 141-143 °C. IR (KBr): 1738, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 5.47 (s, 1H, H-lactam ring), 6.47 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.65 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.76 (d, *J* = 15.9 Hz, 1H, α-H (styryl), 7.09-7.87 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 59.6, 64.8, 120.0, 122.5, 124.1, 125.3, 126.2, 127.3, 127.9, 128.1, 128.7, 132.3, 133.2, 134.7, 140.4, 165.6, 170.6. MS *m/z* 531 $(M)^+$. Anal. Calcd for $C_{34}H_{23}ClN_2O_3$: C, 74.64; H, 4.37; N, 5.28. Found: C, 74.61; H, 4.32; N, 5.21.

4h. 2-[1-(4-Fluorophenyl)-4-oxo-2,2-distyrylazetidin-3-yl]isoindole-1,3-dione

White solid. mp 152-154 °C. IR (KBr): 1732, 1518 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 5.46 (s, 1H, H-lactam ring), 6.49 (d, *J* = 15.9 Hz, 1H, α-H (styryl), 6.63 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl), 6.75 (d, *J* = 15.9 Hz, 1H, α-H (styryl), 7.11-7.86 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 59.5, 64.7, 120.1, 122.4, 124.3, 125.4, 126.3, 127.4, 127.9, 128.0, 128.5, 132.4, 133.5, 134.8, 140.5, 165.9, 170.5. MS *m/z* 515 $(M)^+$. Anal. Calcd for $C_{34}H_{23}FN_2O_3$: C, 77.03; H, 4.51; N, 5.44. Found: C, 76.96; H, 4.45; N, 5.39.

General methods for the preparation of Compound (4i-l):

A solution of *p*-toluene sulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), 4-nitrophenylacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was further purified by column chromatography on silica gel by using 25% EtOAc/hexane as eluent.

4i. 3-(4-Nitrophenyl)-1-phenyl-4,4-distyrylazetidin-2-one

White solid. Mp 115-117 °C. IR (KBr): 1736, 1530, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 5.46 (s, 1H, H-lactam ring), 6.45 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.59 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl), 6.72 (d, *J* = 15.9 Hz, 1H, α-H (styryl), 7.12-7.85 (m, 19H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 57.2, 61.4, 120.2, 121.6, 122.7, 124.6, 126.4, 127.2, 127.9, 128.2, 129.0, 131.2, 132.2, 133.7, 134.8, 140.7, 170.6. MS *m/z* 473 $(M)^+$. Anal. Calcd for $C_{31}H_{24}N_2O_3$: C, 78.79; H, 5.12; N, 5.93. Found: C, 78.75; H, 5.07; N,

5.86.

4j. 3-(4-Nitrophenyl)-4,4-distyryl-1-*p*-tolylazetidin-2-one

White solid. Mp 109-111 ^{o}C. IR (KBr): 1732, 1528, 1492 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (s, 3H, -CH_3), 5.45 (s, 1H, H-lactam ring), 6.44 (d, J = 16.2 Hz, 1H, α-H (styryl), 6.57 (d, J = 16.2 Hz, 2H, β-H (styryl), 6.71 (d, J =16.2 Hz, 1H, α-H (styryl), 7.09-7.56 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 21.6, 57.3, 61.6, 120.4, 121.7, 122.6, 124.5, 126.6, 127.3, 128.0, 128.4, 129.1, 131.2, 132.4, 133.6, 134.7, 140.8, 170.5. MS *m/z* 487 $(M)^+$. Anal. Calcd for $C_{32}H_{26}N_2O_3$: C, 78.99; H, 5.39; N, 5.76. Found: C, 78.91; H, 5.32; N, 5.71.

4k. 1-(4-Chlorophenyl)-3-(4-nitrophenyl)-4,4-distyryl-azetidin-2-one

White solid. Mp 102-104 ^{o}C. IR (KBr): 1742, 1526, 1488 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.46 (s, 1H, H-lactam ring), 6.45 (d, J = 15.9 Hz, 1H, α-H (styryl), 6.55 (d, J = 15.9 Hz, 2H, β-H (styryl), 6.69 (d, J = 15.9 Hz, 1H, α-H (styryl), 7.12-7.57 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 57.4, 61.5, 120.6, 121.8, 122.7, 124.3, 126.5, 127.4, 127.9, 128.5, 129.0, 131.1, 132.3, 133.4, 134.6, 140.7, 170.6. MS *m/z* 507 $(M)^+$. Anal. Calcd for $C_{31}H_{33}ClN_2O_3$: C, 73.44; H, 4.57; N, 5.53. Found: C, 73.39; H, 4.51; N, 5.46.

4l. 1-(4-Fluorophenyl)-3-(4-nitrophenyl)-4,4-distyrylazetidin-2-one

White solid. Mp 119-121 ^{o}C. IR (KBr): 1738, 1530, 1495 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.42 (s, 1H, H-lactam ring), 6.46 (d, J = 15.9 Hz, 1H, α-H (styryl)), 6.54 (d, J = 15.9 Hz, 2H, β-H (styryl)), 6.71 (d, J = 15.9 Hz, 1H, α-H (styryl)), 7.11-7.55 (m, 18H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 57.3, 61.4, 120.5, 121.6, 122.8, 124.4, 126.6, 127.2, 127.7, 128.4, 129.1, 130.9, 132.4, 133.6, 134.5, 140.8, 170.5. MS *m/z* 491 $(M)^+$. Anal. Calcd for $C_{31}H_{33}FN_2O_3$: C, 75.90; H, 4.73; N, 5.71. Found: C, 75.86; H, 4.69; N, 5.65.

General methods for the preparation of compound (5a-d):

A solution of *p*-toluenesulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), methylsulfanylacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product thus obtained was further purified by column chromatography on silica gel by using 10% EtOAc/hexane as eluent.

5a. 3-Methylsulfanyl-1-phenyl-4,4-distyrylazetidin-2-one

Yellow solid. Mp 102-104 ^{o}C. IR (KBr): 1751, 1530, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.19 (s,

3H, -SCH_3), 4.31 (s, 1H, H-lactam ring), 6.51 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.75 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.93 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.20-7.47 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.1, 57.5, 63.7, 120.5, 123.3, 124.4, 126.2, 127.1, 127.5, 128.2, 128.7, 134.7, 140.7, 170.2. MS *m/z* 398 $(M)^+$. Anal. Calcd for $C_{26}H_{23}NOS$: C, 78.55; H, 5.83; N, 3.52. Found: C, 78.51; H, 5.76; N, 3.48.

5b. 3-Methylsulfanyl-4,4-distyryl-1-*p*-tolylazetidin-2-one

Yellow solid. mp 108-110 ^oC. IR (KBr): 1748, 1528, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.19 (s, 3H, -SCH_3), 2.29 (s, 3H, -CH_3) 4.30 (s, 1H, H-lactam ring), 6.49 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.73 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.92 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.21-7.49 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 21.9, 57.6, 63.6, 120.4, 123.2, 124.3, 126.1, 127.0, 127.6, 128.3, 128.9, 134.6, 140.8, 170.4. MS *m/z* 412 $(M)^+$. Anal. Calcd for $C_{27}H_{25}NOS$: C, 78.80; H, 6.17; N, 3.40. Found: C, 78.72; H, 6.13; N, 3.34.

5c. 1-(4-Chlorophenyl)-3-methylsulfanyl-4,4-distyrylazetidin-2-one

Yellow solid. Mp 115-117 ^oC. IR (KBr): 1755, 1532, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, -SCH_3), 4.32 (s, 1H, H-lactam ring), 6.48 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 6.72 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.91 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 7.18-7.46 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 57.5, 63.4, 120.3, 123.3, 124.4, 126.2, 127.1, 127.5, 128.2, 128.7, 134.5, 140.7, 170.3. MS *m/z* 432 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNOS$: C, 72.29; H, 5.13; N, 3.29. Found: C, 72.26; H, 5.09; N, 3.25.

5d. 1-(4-Fluorophenyl)-3-methylsulfanyl-4,4-distyrylazetidin-2-one

Yellow solid. Mp 105-107 ^oC; IR (KBr): 1745, 1527, 1498 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H, -SCH_3), 4.31 (s, 1H, H-lactam ring), 6.47 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.74 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.93 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.20–7.49 (m, 14H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 57.4, 63.5, 120.2, 123.4, 124.5, 126.3, 127.0, 127.4, 128.1, 128.6, 134.4, 140.5, 170.5 . MS *m/z* 416 $(M)^+$. Anal. Calcd for $C_{26}H_{22}FNOS$: C, 75.15; H, 5.34; N, 3.37. Found:C, 75.11; H, 5.29; N, 3.31.

General methods for the preparation of compound (5e-h):

A solution of *p*-toluenesulphonyl chloride (3.5 mmol) in dry CH_2Cl_2 was added dropwise to a solution of azatriene **1** (2 mmol), methoxyacetic acid (2 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 under stirring at room temperature. After the complete addition, the solution was stirred for an additional 15 min. Completion of reaction was confirmed by TLC. Water was added to the reaction mixture and organic layer was separated. Organic layer was washed twice with saturated aqueous solution of Na_2CO_3, separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the

crude product thus obtained was further purified by column chromatography on silica gel by using 20% EtOAc/hexane as eluent.

5e. 3-Methoxy-1-phenyl-4,4-distyrylazetidin-2-one

Yellow solid. mp 122-124 ^{o}C. IR (KBr): 1738, 1532, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.23 (s, 3H, -OCH_3), 4.33 (s, 1H, H-lactam ring), 6.52 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.74 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.91 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.21–7.48 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 51.4, 57.4, 63.6, 121.2, 123.4, 124.6, 126.3, 127.2, 127.6, 128.1, 128.9, 134.6, 140.8, 170.4. MS *m/z* 382 $(M)^+$. Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.80; H, 6.01; N, 3.62.

5f. 3-Methoxy-4,4-distyryl-1-*p*-tolylazetidin-2-one

Yellow solid. Mp 128-130 ^{o}C. IR (KBr): 1735, 1530, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.27 (s, 3H, -CH_3), 3.21 (s, 3H, -OCH_3), 4.32 (s, 1H, H-lactam ring), 6.51 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 6.77 (d, *J* = 16.2 Hz, 2H, *β*-H (styryl)), 6.94 (d, *J* = 16.2 Hz, 1H, α-H (styryl)), 7.19–7.49 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.7, 51.4, 57.7, 63.4, 121.4, 123.6, 124.8, 126.7, 127.3, 127.7, 128.2, 129.0, 134.7, 140.9, 170.5. MS *m/z* 396 $(M)^+$. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.96; H, 6.31; N, 3.48.

5g. 1-(4-Chlorophenyl)-3-methoxy-4,4-distyrylazetidin-2-one

Yellow solid. Mp 135-137 ^{o}C. IR (KBr): 1738, 1512, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (s, 3H, -OCH_3), 4.31 (s, 1H, H-lactam ring), 6.49 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.75 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.93 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.18–7.47 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 51.4, 57.8, 63.6, 121.5, 123.5, 124.7, 126.7, 127.4, 127.9, 128.3, 129.1, 134.8, 140.7, 170.4. MS *m/z* 416 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNO_2$: C, 75.08; H, 5.33; N, 3.37. Found: C, 75.01; H, 5.27; N, 3.31.

5h. 1-(4-Fluorophenyl)-3-methoxy-4,4-distyrylazetidin-2-one

Yellow solid. Mp 128-130 ^{o}C. IR (KBr): 1742, 1517, 1498 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.22 (s, 3H, -OCH_3), 4.33 (s, 1H, H-lactam ring), 6.50 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 6.76 (d, *J* = 15.9 Hz, 2H, *β*-H (styryl)), 6.92 (d, *J* = 15.9 Hz, 1H, α-H (styryl)), 7.19–7.48 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 51.3, 57.7, 63.5, 121.4, 123.6, 124.8, 126.6, 127.3, 127.9, 128.4, 129.2, 134.7, 140.8, 170.5. MS *m/z* 400 $(M)^+$. Anal. Calcd for $C_{26}H_{22}FNO_2$: C, 75.18; H, 5.55; N, 3.51. Found: C, 75.11; H, 5.51; N, 3.48.

General methods for the preparation of Compound (6a-e):

A solution of **5a-e** in toluene was heated at reflux for 8 h and then concentrated in vacuo. Purification of the residue by column chromatography on silica gel by using 40% EtOAc/hexane as eluent resulted in the

isolation of pure product.

6a. 3-Methylsulfanyl-1,4-diphenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 182-184 ^{o}C. IR (KBr): 1682, 1527 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.35 (s, 3H, -SCH_3-), 3.59 (d, J = 12.3 Hz, 1H, H^3), 3.86 (d, J = 12.3 Hz, 7.1 Hz, 1H, H^4), 5.79 (d, J = 7.1 Hz, 1H, H^5), 6.11 (d, J = 15.9 Hz, 1H, H^7), 6.79 (d, J = 15.9 Hz, 1H, H^8), 7.09-7.41 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 15.6, 46.7, 56.8, 110.7, 122.8, 126.4, 127.3, 127.8, 128.1, 128.3, 128.5, 129.0, 129.6, 130.9, 135.6, 136.4, 137.6, 139.3, 141.6, 171.5. MS *m/z* 367 $(M)^+$. Anal. Calcd for $C_{26}H_{23}NOS$: C, 78.55; H, 5.83; N, 3.52. Found: C, 78.51; H, 5.78; N, 3.47.

6b. 3-Methylsulfanyl-4-phenyl-6-styryl-1-p-tolyl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 178-180 ^{o}C. IR (KBr): 1680, 1531 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (s, 3H, -CH_3), 2.34 (s, 3H, -SCH_3), 3.58 (d, J = 12.5 Hz, 1H, H^3), 3.86 (dd, J = 12.5 Hz, 7.3 Hz, 1H, H^4), 5.78 (d, J = 7.3 Hz, 1H, H^5), 6.11 (d, J = 15.9 Hz, 1H, H^7), 6.78 (d, J = 15.9 Hz, 1H, H^8), 7.08–7.42 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 15.5, 46.5, 56.7, 110.8, 122.7, 126.5, 127.4, 127.9, 128.1, 128.3, 128.6, 129.0, 129.5, 131.0, 135.7, 136.5, 137.7, 139.4, 141.7, 171.6. MS *m/z* 412 $(M)^+$. Anal. Calcd for $C_{27}H_{25}NOS$: C, 78.80; H, 6.12; N, 3.40. Found: C, 78.76; H, 6.06; N, 3.37.

6c. 1-(4-Chlorophenyl)-3-methylsulfanyl-4-phenyl-6-styryl-3,4-dihydro-1*H*-pyridin-2-one

Yellow solid. Mp 179-182 ^{o}C. IR (KBr): 1682, 1529 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.35 (s, 3H, -SCH_3-), 3.57 (d, J = 12.6 Hz, 1H, H^3), 3.85 (dd, J = 12.6 Hz, 7.2 Hz, 1H, H^4), 5.77 (d, J = 7.2 Hz, 1H, H^5), 6.10 (d, J = 15.9 Hz, 1H, H^7), 6.77 (d, J = 15.9 Hz, 1H, H^8), 7.07-7.41 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 15.4, 46.4, 56.5, 110.7, 122.6, 126.4, 127.5, 127.9, 128.1, 128.3, 128.7, 129.0, 129.6, 131.1, 135.6, 136.4, 137.8, 139.5, 141.6, 171.7. MS *m/z* 432 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNOS$: C, 72.29; H, 5.13; N, 3.24. Found: C, 72.24; H, 5.09; N, 3.16.

6d. 1-(4-Fluorophenyl)-3-methylsulfanyl-4-phenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

Yellow solid. Mp 175-177 ^{o}C. IR (KBr): 1679, 1537 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3) δ_H: 2.33 (s, 3H, -SCH_3-), 3.56 (d, J = 12.4 Hz, 1H, H^3), 3.87 (dd, J = 12.4 Hz, 7.1 Hz, 1H, H^4), 5.76 (d, J = 7.1 Hz, 1H, H^5), 6.12 (d, J = 15.9 Hz, 1H, H^7), 6.78 (d, J = 15.9 Hz, 1H, H^8), 7.08-7.43 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 15.5, 46.6, 56.6, 110.8, 122.7, 126.5, 127.4, 127.8 128.0, 128.3, 128.7, 129.0, 129.6, 131.2, 135.5, 136.6, 137.7, 139.6, 141.5, 171.6. MS *m/z* 416 $(M)^+$. Anal. Calcd for $C_{26}H_{22}FNOS$: C, 75.15; H, 5.34; N, 3.37. Found: C, 75.10; H, 5.29; N, 3.31.

General methods for the preparation of Compound (6e-h):

A solution of **5e-h** in toluene was heated at reflux for 8 h and then concentrated in vacuo. Purification of the residue by column chromatography on silica gel by using 55% EtOAc/hexane as eluent resulted in the isolation of pure product

6e. 3-Methoxy-1,4-diphenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

White solid. Mp 137-139 ^{o}C. IR (KBr): 1678, 1532 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (s, 3H, OCH_3), 3.55 (d, J = 12. 2Hz, 1H, H^3), 3.86 (dd, J = 12.6 Hz, 7.2 Hz, 1H, H^4), 5.75 (d, J = 7.2 Hz, 1H, H^5), 6.11 (d, J = 15.9 Hz, 1H, H^7), 6.77 (d, J = 15.9 Hz, 1H, H^8), 7.07-7.44 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.5, 51.1, 56.5, 110.7, 122.6, 126.4, 127.3, 127.7 128.0, 128.2, 128.8, 129.0, 129.5, 131.1, 135.7, 136.5, 137.8, 139.5, 141.4, 171.5. MS *m/z* 382 $(M)^+$. Anal. Calcd for $C_{26}H_{22}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.79; H, 6.01; N, 3.61.

6f. 3-Methoxy-4-phenyl-6-styryl-1-p-tolyl-3,4-dihydro-*1H*-pyridin-2-one

White solid. Mp 132-134 ^{o}C. IR (KBr): 1680, 1527 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.29 (s, 3H, $-CH_3$), 3.23 (s, 3H, OCH_3), 3.54 (d, J = 12.6 Hz, 1H, H^3), 3.84 (dd, J = 12.6 Hz, 7.1 Hz, 1H, H^4), 5.76 (d, J = 7.1 Hz, 1H, H^5), 6.10 (d, J = 15.9 Hz, 1H, H^7), 6.76 (d, J = 15.9 Hz, 1H, H^8), 7.08–7.43 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.9, 46.6, 51.2, 56.6, 110.8, 122.7, 126.5, 127.2, 127.6, 128.1, 128.3, 128.7, 129.1, 129.4, 131.2, 135.6, 136.4, 137.7, 139.4, 141.3, 171.4. MS *m/z* 382 $(M)^+$. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.94; H, 6.32; N, 3.49.

6g. 1-(4-Chlorophenyl)-3-methoxy-4-phenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

White solid. Mp 126-128 ^{o}C. IR (KBr): 1680, 1527 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (s, 3H, OCH_3), 3.56 (d, J = 12.3 Hz, 1H, H^3), 3.85 (dd, J = 12.3 Hz, 7.4Hz, 1H, H^4), 5.77 (d, J = 7.4 Hz, 1H, H^5), 6.11 (d, J = 15.9 Hz, 1H, H^7), 6.75 (d, J = 15.9 Hz, 1H, H^8), 7.07–7.42 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.4, 51.1, 56.7, 110.7, 122.6, 126.5, 127.1, 127.7, 128.1, 128.3, 128.6, 129.1, 129.5, 131.1, 135.7, 136.5, 137.6, 139.5, 141.4, 171.5. MS *m/z* 416 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNO_2$: C, 75.08; H, 5.33; N, 3.37. Found: C, 75.01; H, 5.27; N, 3.31.

6h. 1-(4-Fluorophenyl)-3-methoxy-4-phenyl-6-styryl-3,4-dihydro-*1H*-pyridin-2-one

White olid. Mp 121-123 ^{o}C. IR (KBr): 1682, 1527 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.23 (s, 3H, OCH_3), 3.55 (d, J = 12.2 Hz, 1H, H^3), 3.86 (dd J = 12.2 Hz, 7.2 Hz, 1H, H^4), 5.76 (d, J = 7.2 Hz, 1H, H^5), 6.10 (d, J = 15.9 Hz, 1H, H^7), 6.74 (d, J = 15.9 Hz, 1H, H^8), 7.08–7.43 (m, 14H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 46.5, 51.3, 56.6, 110.5, 122.6, 126.4, 127.1, 127.7, 128.1, 128.3, 128.6, 129.1, 129.5, 131.1, 135.7, 136.5, 137.6, 139.5, 141.4, 171.5. MS *m/z* 416 $(M)^+$. Anal. Calcd for $C_{26}H_{22}ClNO_2$: C, 75.08; H, 5.33; N, 3.37. Found: C, 75.01; H, 5.27; N, 3.31.

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