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Triflic acid promoted Fries rearrangement of C-3 vinyl/isopropenyl-azetidin-2-ones: Single-pot synthesis of C-3 functionalized-2-aryl-2,3-dihydro-quinoline-4(1*H*)-ones

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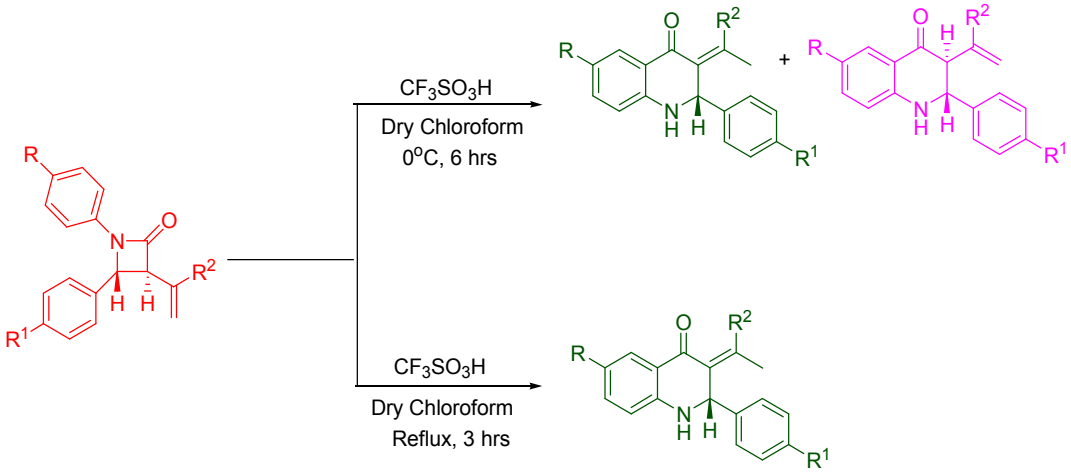

Single-pot synthesis of C-3 functionalized-2-aryl-2,3-dihydro-quinoline-4(1*H*)-ones with stability profile validation using density functional theory (DFT) calculations.

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Triflic acid promoted Fries rearrangement of C-3 vinyl/isopropenyl-azetidin-2-ones: Single-pot synthesis of C-3 functionalized-2-aryl-2,3-dihydro-quinoline-4(1*H*)-ones

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Abstract—*β*-lactam-synthon-interceded synthesis of C-3 functionalized 2-aryl-2,3-dihydro-quinoline-4(1*H*)-ones has been described *via* Fries rearrangement of C-3 vinyl/isopropenyl substituted *β*-lactams. The reaction at 0°C resulted in the isolation of a tautomeric mixture while the preferential formation of the conjugated product was observed at higher temperature. The density functional theory (DFT) calculations and molecular dynamics (MD) simulations were additionally performed to explain the preferential formation of product **2** over **3**.The proposed mechanism was further validated via base-induced isomerisation of the mixture of **2a** and **3a**.

Introduction

Quinoline-4-ones represent an important class of heterocyclic scaffolds that have engendered much interest due to their various biological and pharmacological activities.[1] This heterocyclic unit also constitute an integral component in drugs used for the treatment of neurodegenerative diseases, sleep disorders and in antibiotics *viz.* norfloxacin and ciprofloxacin.[2] The synthetic accessibility and possibility of functionalization at varied positions in quinoline-4-ones exemplify an elegant platform for the design of combinatorial libraries[3] of functionally enriched scaffolds with a range of pharmacological profiles.[4] They are also considered as attractive precursors for the synthesis of medicinally imperative molecules such as non-steroidal androgen receptor antagonists,[5] the antimalarial drug Chloroquine[6] and martinellines with antibacterial activity.[7] 2-Aryl-2,3-dihydroquinolin-4(*1H*)-ones are present in many natural and non-natural compounds and considered as aza-analogs of flavanones.[8]

A number of synthetic protocols have been reported for the synthesis of 2,3-dihydroquinolin-4(1*H*)-ones of which the most widely used pathway is the isomerization of substituted 2'-aminochalcones in the presence of NaOEt,[9a] H_3PO_4,[9b] montmorillonite,[9c] $InCl_3$,[9d] silica gel supported $TaBr_5$,[9e] silica gel supported $NaHSO_4$,[9f] $ZnCl_2$,[9g] Silica-supported $Yb(OTf)_3$,[9h] PEG-400[9i] or alumina supported-$CeCl_3 \cdot 7H_2O$-NaI.[9j] The strategies *viz.* Pd-catalyzed allylic amination-thiazolium salt catalyzed Stetter reaction,[10a] multicomponent cyclocarbonylation of *o*-iodoanilines with allenes and CO using palladium complex in ionic liquids[10b] and Lewis acid-promoted one-pot multistep transformations of 2-alkynylanilines or -benzamides with aldehydes[11] have recently appeared in literature for accessing 3-substituted 2,3-dihydroquinolin-4(1*H*)-ones. However, most of the reported synthetic protocols are invariably associated with significant drawbacks including the use of highly corrosive reagents, long reaction times, tedious work up procedures, need of large amount of catalyst and specialized solvents which limit their synthetic applicability.

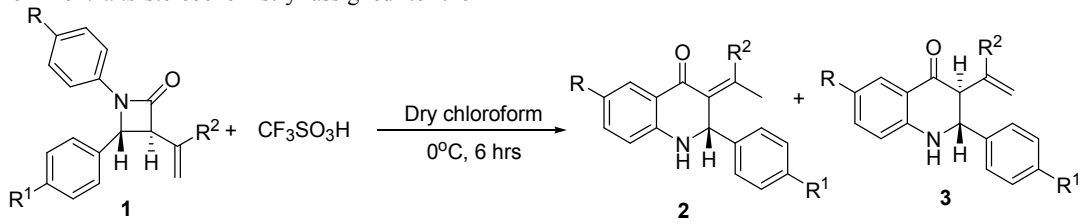
The class of *β*-lactam antibiotics is generally recognized as a cornerstone of human health care due to the unparalleled clinical efficacy and safety of this type of antibacterials.[12] Besides their biological relevance as potential antibiotics, *β*-lactams have also acquired a prominent place in organic chemistry as synthons, and provide highly efficient routes to a variety of non-protein amino acids, oligopeptides, peptidomimetics, nitrogen-heterocycles, as well as biologically active natural and unnatural products of medicinal interest such as indolizidine alkaloids, paclitaxel, docetaxel, taxoids, cyptophycins, lankacidins etc.[13]

A straight forward route towards the synthesis of quinoline-4-ones *via* triflic acid assisted Fries rearrangement of *N*-aryl-*β*-lactams has been reported by Tepe and co-workers.[14] The ring expansion observed in this case was solely ascribed to the inherent ring strain in *β*-lactam ring as *γ*-lactam failed to undergo rearrangement under the reaction conditions. The above protocol has been recently extended by our group in the synthesis of benzo[b]-azocinon-6-ones *via* tandem Michael addition–Fries rearrangement of sorbyl anilides[15] as well as in the single-pot synthesis of 2-aryl-quinolin-4(3*H*)-ones[16e] through Fries rearrangement of 3-dienyl-*β*-lactams. In continuation with our synthetic endeavours with the *β*-lactam ring [16] and in view of the lack of convenient approaches for the synthesis of C-3 functionalized quinolin-4(1*H*)-ones, the present manuscript describes single-pot synthesis of C-3 functionalized quinolin-4(1*H*)-ones *via* triflic acid promoted Fries rearrangement of C-3 vinyl/isopropenyl substituted *β*-lactams. Additionally, the DFT calculations and MD simulations were performed to investigate the stability profiles of the synthetic compounds (**2a** and **3a**).

Result and Discussion

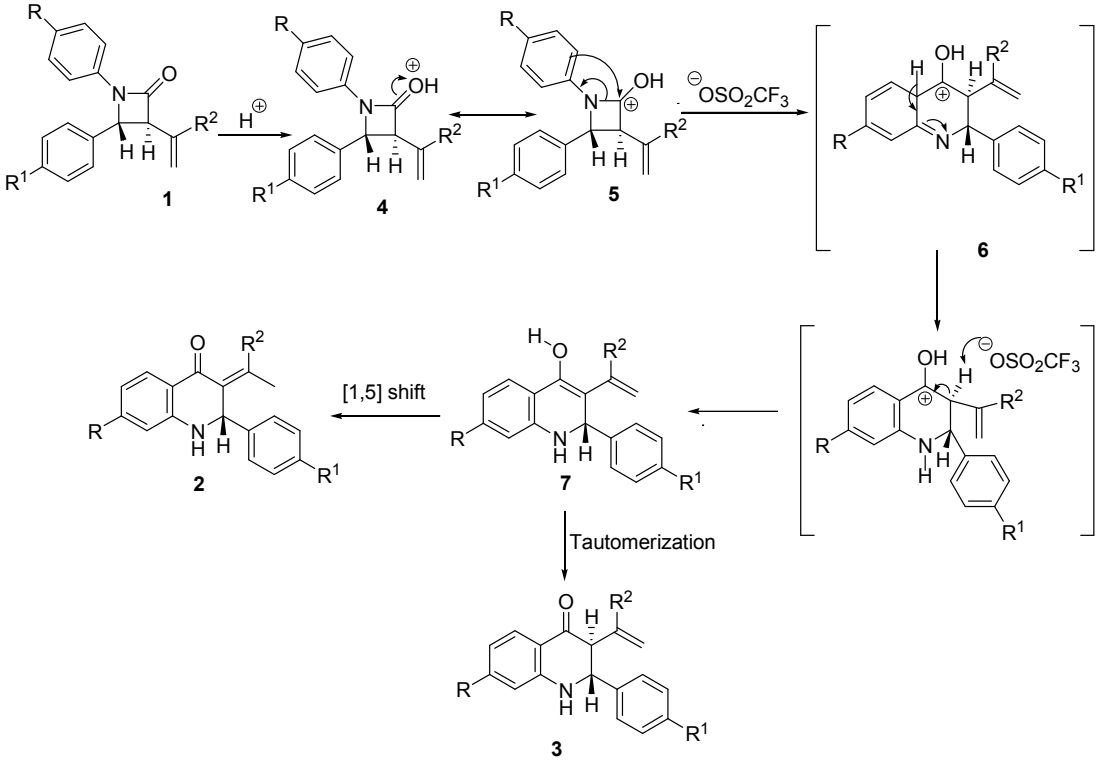
The precursors *viz.* 3-vinyl/isopropenyl-1,4-diaryl-azetidin-2-ones **1a-h** were prepared *via.* Staudinger reaction of corresponding imines with vinyl/isopropenyl ketene generated *in situ* from crotonic/3-methylcrotonic acid chloride in the presence of triethylamine.The *trans*-stereochemistry to compound **1** was assigned on the basis of coupling constant *J*=2.1Hz between H-3 and H-4.[17] The treatment of C-3vinyl/isopropenyl *β*-lactams **1a-h** (3.0 *eq*)with 1.0 *eq* of trifloromethanesulphonic acid (triflic acid) in dry chloroform at 0°C for 6 hrs resulted in the formation of a mixture of 3-ethylidene/isopropylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **2a-h** and3-vinyl/isopropenyl-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **3a-h** which was separated by column

chromatography using a mixture of (Hexane: Ethylacetate 90:10) for compound **2** and (Hexane: Ethylacetate 75:25) for compound **3** (Scheme 1).The The *trans*-stereochemistry assigned to the product**3** was on the basis of coupling constant *J*=6.0 Hz between H-2 and H-3.[18]



Entry	R	R^1	R^2	% age Yield of 2	% age Yield of 3
2a + 3a	CH_3	H	H	54	33
2b + 3b	H	H	H	52	34
2c + 3c	Cl	H	H	53	35
2d + 3d	CH_3	CH_3	H	55	31
2e + 3e	H	H	CH_3	53	34
2f + 3f	Cl	H	CH_3	52	35
2g + 3g	CH_3	H	CH_3	51	33
2h + 3h	CH_3	CH_3	CH_3	54	32

Scheme 1: Synthesis of 2-aryl-2,3-dihydro-1*H*-quinolin-4-ones**2** and **3**



Scheme 2: Plausible mechanism for the formation of 2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **2** and **3**

The plausible mechanism for the above transformations is believed to involve an initial protonation of 3-vinyl/isopropenyl-*β*-lactam **1** generating the carbenium ion intermediate **5**. The intermediate **5** readily undergoes Fries rearrangement *via* an *ortho* attack of the aromatic substituent on the nitrogen atom, resulting in a ring expanded intermediate **6**. Its aromatization accompanied by proton abstraction generates the intermediate **7** which undergoes [1,5] sigmatropic shift/ tautomerization to yield a mixture of 3-ethylidene/isopropylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **2a-h** and3-vinyl/isopropenyl-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **3a-h** respectively, as shown in Scheme 2.

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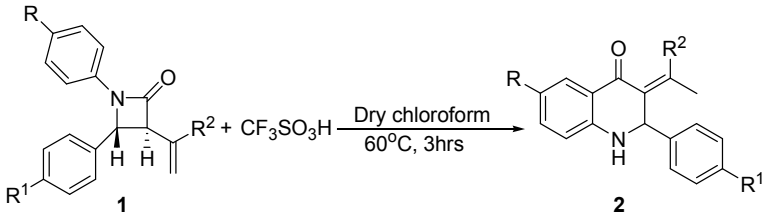


Entry	R	R^1	R^2	Reaction Time (hrs)	% age Yield of 2
2a	CH_3	H	H	3.0	78
2b	H	H	H	3.3	75
2c	Cl	H	H	3.2	77
2d	CH_3	CH_3	H	3.1	76
2e	H	H	CH_3	3.2	79
2f	Cl	H	CH_3	3.1	77
2g	CH_3	H	CH_3	3.3	74
2h	CH_3	CH_3	CH_3	3.4	76

Scheme 3: Synthesis of 3-ethylidene/isopropylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones **2** under reflux in chloroform

Interestingly, the similar reactions when carried out under reflux in dry chloroform led to the exclusive formation of **2a-h** in excellent yields without the formation of **3** even in traces as confirmed by the ^{1}HNMR spectrum of crude reaction mixture (Scheme 3).

In order to unequivocally confirm the preferential formation of **2** over **3**, the representative compounds **2a** and **3a** were geometrically optimized in gas phase and in self-consistent reaction-model (SCRF) chloroform model using B3LYP/6-31+G(d) basis set at DFT level (details in method section). The Gaussian computer program[19] was used for these optimizations. The electronic energies (△E) and free energies (△G) of **3a** and intermediate (**7a**) computed relative to **2a** are depicted in the Table 1.

Table 1: The corrected relative electronic energies (in kcalmol^{-1}) and free energies of 2a, 3a, TS^{2a} and TS^{3a} with respect to intermediate 7a, computed at DFT level.

Compound	Gas Phase		$CHCl_3$ (PCM)	
	△ E	△G	△E	△G
7a	0	0	0	0
2a	-13.5	-15.7	-15.4	-16.2
3a	-4.5	-4.6	-5.8	-4.7
TS^{2a}	10.9	11.1	10.4	12.0
TS^{3a}	49.0	48.2	47.8	48.4

Compound **2a** was clearly found to be energetically more favorable than **3a** both in gas phase (9 kcalmol^{-1}) and in chloroform (9.6 kcalmol^{-1}), as depicted in Table 1. The computed free energies (△G) also further favoured the formation of **2a** over **3a**, as depicted in Table 1. Additionally, the associated energy barriers for conversion of intermediate **7a** (Scheme 2) to products (**2a** and **3a**) at experimental temperatures (273K and 320 K) were calculated at the same level of theory in gas phase. These results show that the energy barrier for formation of product **2a** was significantly lower (38 kcalmol^{-1}, **Figure 1**) at 320 K, and supports the preferential formation of product **2a** over **3a**, in accordance with the experimental observations. The DFT calculations performed at 273 K did not produce any change in the transition state energies, and could not explain the experimental formation of minor product (**3a**) at low temperature probably due to their gas phase nature. In order to investigate the effect of solvent, the transition energy barriers were computed at same level of theory using PCM model of chloroform. A small decrease in TS energy barrier (dotted lines, **Figure 1**) was observed for both products in the presence of solvent model, suggesting the role of solvent in their stability. However, results were still inadequate to explain the experimental formation of **3a** in lower percentages at 0^{o}C. Similar calculations under explicit solvent conditions could have provided deeper insights into their stability profiles; however the non-feasibility of such calculations at quantum mechanical level in Gaussian program limited our further study.

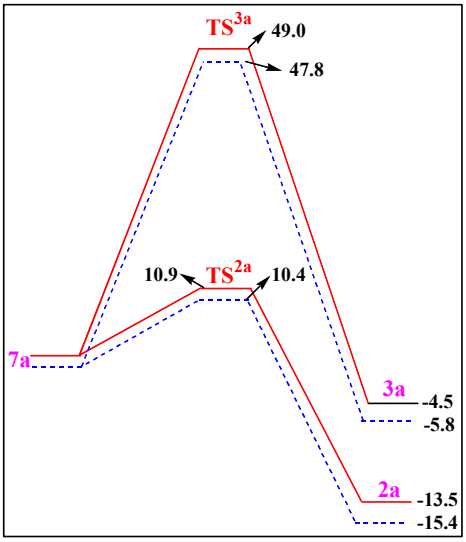


Figure 1: Potential energy diagram for the conversion of intermediate (**7a**) to products **2a** and **3a**, both in gas phase (solid lines, in red) and in chloroform (dotted lines, in blue). All energies are in kcalmol^{-1}.

Since, the three dimensional (3D) structural orientation and stability of organic molecules are severely affected by the physical existence of solvent molecules, it was thought worthwhile to investigate the dynamics of both compounds (**2a** and **3a**) in the presence of explicit solvent molecules. Considering the inability of DFT calculations to represent explicit solvent effects, the molecular dynamics (MD) simulations were used due to their extensive applications in peptide chemistry coupled with their successful recent utilization in our research group.[20] Accordingly, both compounds **(2a** and **3a**) were soaked in the boxes of chloroform molecules (see method section) to mimic the experimental solvent conditions. MD^{2a} and MD^{3a} simulations for compounds **2a** and **3a**, respectively, were subsequently performed using the AMBER program.[21] The quality of MD simulations was first assessed by plotting different thermodynamic properties such as Total Energy (TE, Figure 2), Temperature (T) and Density, as a function of simulation time. The average fluctuation of T around 273 K (Figure A, supplementary data), and of density around 1.46 g/ml (Figure B, supplementary data) suggested the stable and accuracy of the simulations performed. Moreover, the average fluctuation of TE for **2a** (in green) was comparatively lower than **3a** (in blue) throughout the progress of MD simulation, and suggests the better stability of former than the later.

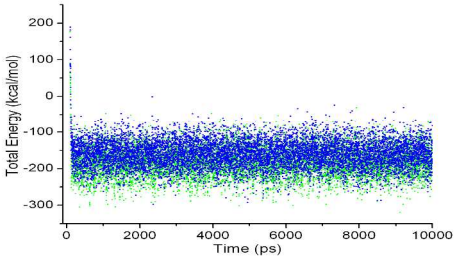
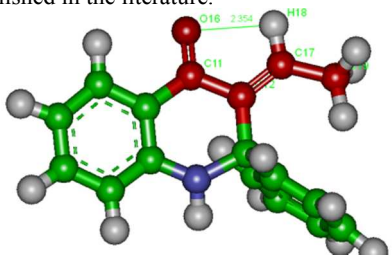
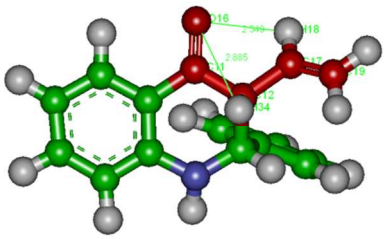


Figure 2: Total Energy profile for the compound MD^{2a} (in green) and MD^{3a} (in blue).

The lowest energy structures (solvent stripped off) of both compounds (**2a** and **3a**) were further extracted from their respective trajectories (MD^{2a} and MD^{3a}) using the PTRAJ module in AMBER program, and are pictorially represented in **Figure 3**. The inter-atomic distance between carbonyl oxygen (O16) and olefinic hydrogen (H18) in **2a** was also comparatively smaller (2.35Å, Figure 3a) than those present in **3a** (2.54Å, Figure 3b), clearly suggesting the stronger H-bond interactions between the two atoms. The additional interaction between O16 and tautomeric proton (H34) in **3a** was also relatively weaker (2.885Å, Figure 4b). The presence of these unusual hydrogen bond interactions (CO…HC-) has already been established in the literature.[22]



(a)



(b)

Figure 3: Lowest energy structure of compound **2a** (a) and **3a** (b) extracted from the simulations MD^{2a} and MD^{3a}, respectively.

Figure 4 represent the progress of inter-atomic distance (O16-H18) during the sampling process in the trajectories MD^{2a} (in black) and MD^{3a} (in red). Clearly, a strong hydrogen bond interaction fluctuating around 2.5 Å (in black, Figure 5) was observed immediately from the start of the simulation (MD^{2a}), and sustained throughout the progress of the trajectory. Although similar bond distances (~2.5 Å) in equilibrium with larger ones (~4.0Å), as depicted in Figure 4 (in red), were present in the conformations of **3a** sampled during the first 5ns segment of the trajectory MD^{3a}, the oscillations increased rapidly (3.0-4.3Å) during the last 5ns part of the trajectory. The faster C12-C17 bond rotations attributed to its low conformational energy barrier could be the reason for these larger fluctuations in **3a** and probably decreasing its stability compared to its structural analogue **2a**.

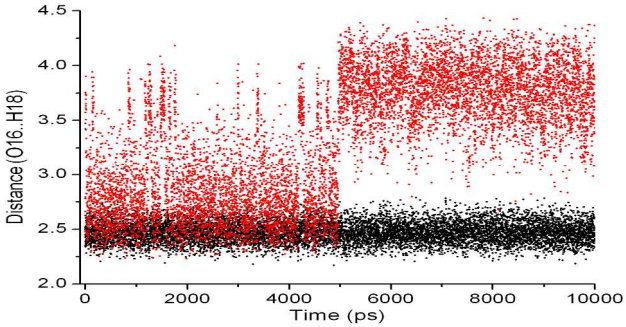


Figure 4: Evolution of distance (O16-H18) in the trajectories MD^{2a} (in black) and MD^{3a} (in red). Both red and black dots represent the computed distances in the simulations.

Similar hydrogen bond (O16-H18) was further monitored at higher temperature by performing two additional MD simulations for both compounds at 320 K under explicit solvent conditions, and is depicted in Figure 5. Clearly, the distance (O16-H18), in case of **3a**, was unstable and fluctuates between 2.8-4.3Å in all the sampled conformations (in red, Figure 5). The average fluctuation in case of compound **2a**, on other hand, was stable and oscillates around 2.85Å (in black, Figure 5) throughout the progress of the MD trajectory.

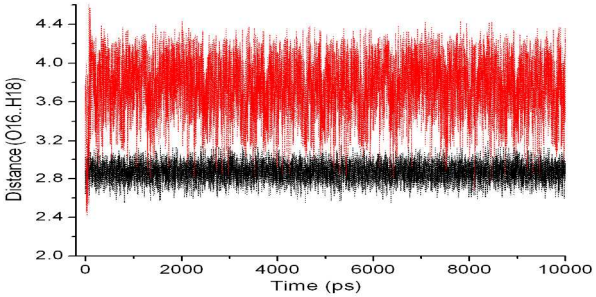


Figure 5: The progress of distance (O16-H18) in the trajectories MD^{2a} (in black) and MD^{3a} (in red) performed at 320K.

The results were further substantiated by studying the evolution of dihedral angle, C11-C12-C17-C19 (highlighted in red, Figure 3) for the sampled conformations of both trajectories (MD^{2a} and MD^{3a}), and is diagrammatically depicted in the Figure 6. As evident, the dihedral angle was quite fixed in case of compound **2a** (in black, Figure 6), exhibiting average fluctuations at 175° and -175°. Although, similar average angle fluctuations (175, -175) were attained by the conformations of compound **3a**, the extent of oscillations was comparatively higher (in red, Figure 6) than those observed in **3a** due to fast C-C bond rotations.

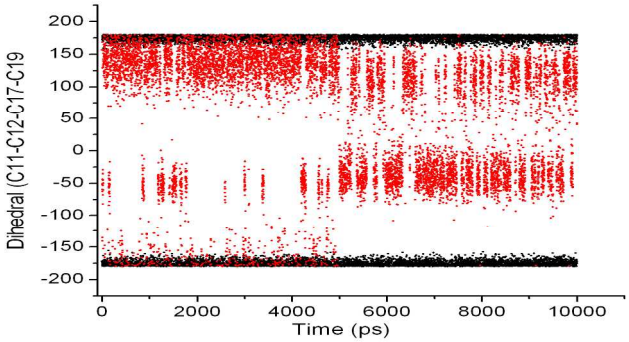
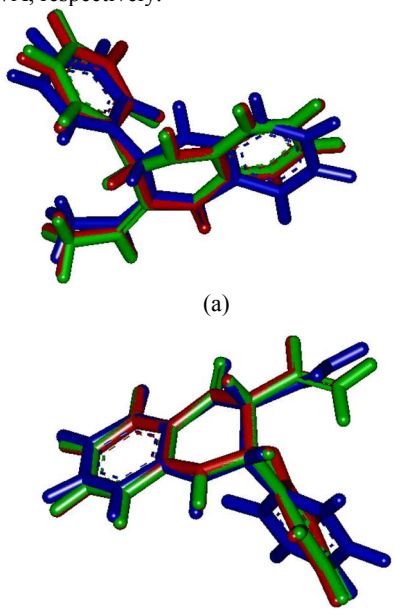


Figure 6: The progress of dihedral angle C11-C12-C17-C19 in the trajectories MD^{2a} (in black) and MD^{3a} (in red).

Finally, a comparison of MD studies was performed with the DFT results. For this purpose, the DFT optimized structures of **2a** and **3a** were overlaid on the LE structures of MD using Discovery Studio program,[23] and are depicted in Figures 8a-b. The calculated root mean square deviations (RMSDs) of MD structures (in blue, Figures 7a-b) of **2a** and **3a** relative to their gas phase structures (in green , Figures 7a-b) were found to be around 0.56Å and 0.80Å, respectively, clearly indicating structural resemblances between them. Although, the MD structures and DFT optimized structures fit well on each other (RMSD <1Å), the plane of quinoline ring in MD structures (in blue, Figures 7a-b) was slightly folded to bring the carbonyl and olefinic hydrogen (H18) in closer vicinity for potential hydrogen bond interaction. The presence of chloroform molecules probably has stabilized these folded geometries of **2a** and **3a**. The gas phase (in green, Figures 7a-b) and implicit chloroform structures (in red, Figures 7a-b) of **2a** and **3a**, overlapped perfectly well on each other showing their RMSDs around 0.14 Å and 0.07Å, respectively.



(a)

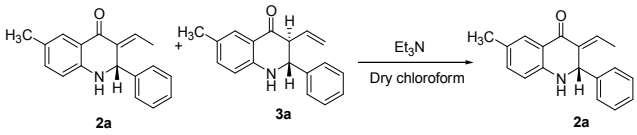
(b)

Figure 7: (a) Overlay of the optimized structures of **2a** and **3a** obtained in gas phase (in green) and in implicit chloroform model (in red) at DFT level, and in explicit chloroform from MD simulations (in blue).

Based on DFT results, it is believed that the requirement of high activation energy is one of the major factors responsible for the formation of product 2a as a major or exclusive product in the reaction. Additionally, the MD results suggest that the hydrogen bond interaction between carbonyl oxygen (CO) and hydrogen atom at position 17 (C17), and the double bond (-C12=C17-) could be other factors that determines the stability of the synthetic compounds. In chloroform, the presence of both these factors in the folded geometry of compound **2a** is probably responsible for its formation as a major product under experimental conditions. Similarly, the presence of hydrogen bonding (O16…H18) led to the formation of 3a in lower percentages attributed to the slower C-C bond (C12-C17) rotation at 0°C.

In order to unequivocally validate the proposed mechanism and confirm the isomerization as the principle route governing the formation of mixture of products it was considered worthwhile to stir the reaction mixture in the presence of base like triethylamine which would promote the

formation of thermodynamically stable conjugate 3-ethylidene-6-methyl-2-phenyl-2,3-dihydro-1H-quinolin-4-one**2a**. Thus, the treatment of a mixture of **2a** and **3a** obtained *via* triflic acid promote Fries rearrangement of **1a**, with triethylamine at room temperature for 12 hrs resulted in the exclusive formation of **2a** as confirmed by its superimposable ^{1}H NMR and undepressed mixed melting point with the sample of **2a** obtained earlier (Scheme 4).



Scheme 4: Exclusive formation of **2a** in the presence of triethylamine.

Conclusion:

The present manuscript describes triflic acid promoted synthesis of C-3 functionalized quinolin-4(1*H*)-ones *via* Fries rearrangement of C-3 vinyl-/isopropenyl substituted azetidin-2-ones. The reaction at 0^{o}C invariably resulted in the tautomeric mixture of products with a preference for the formation of the conjugated product. Compound **2a** was found to be energetically more favourable than **3a** on the basis of DFT calculations. Furthermore, the MD studies suggested the folding nature of these structures leading to a potential hydrogen bond interaction between O16-H18 and stability of **2a** and **3a** at 0^{o}C, with greater percentage of the former due to an additional conjugation. At higher temperature, the faster C-C rotation probably destabilizes **3a** leading to exclusive formation of **2a**. The proposed mechanism was further validated via base-induced isomerisation of the mixture of **2a** and **3a**.

Experimental Section

General

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 Brucker-micrOTOF-Q II mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120 mesh).

Computational Method

The full optimization of all molecules, in gas phase and in SCRF chloroform model was performed using B3LYP/6-31+G (d,p) basis set, with the Gaussian 09 program.[19] Vibrational frequency calculations were also carried out to verify the nature of all the stationary points obtained and to calculate the zero-point vibrational energies (ZPVE). Transition states obtained were confirmed by the occurrence of only one imaginary frequency on the potential energy surface.

For MD simulations, the Restrained Electrostatic Potential (RESP) atomic charges consistent with the Amber program were computed for both compounds (**2a** and **3a**) using the General Amber Force Field (GAFF) in AMBER. Molecular dynamics (MD) simulations were performed using the Amber 9.0 program.[21] Before MD; both compounds were soaked in the boxes of chloroform molecules and minimized using 500 steps of steepest descent, followed by 100 steps of conjugate gradient. The equilibration (500 picoseconds) of both systems was subsequently performed at temperatures 273K and 320 K to create uniform density solvent around both compounds using the periodic boundary conditions (PBC). Finally, MD simulations of length 10 nanoseconds were performed at constant temperatures (273K and 320K) and pressure. Total 10000 conformations were obtained by sampling each conformation at the interval of 1 picosecond from each trajectory. The PTRAJ module of AMBER 9.0 was used for the analysis of both MD trajectories.

Typical procedure for the synthesis of 2-aryl-2,3-dihydro-1*H*-quinolin-4-ones 2 and 3:The synthesis of quinolin-4(1*H*)-one was realized by slow addition of triflic acid(10 mmol) to an ice cold solution of *trans*-3-vinyl/isopropenyl-*β*-lactam **1** (30 mmol) in dry chloroform (20 mL) solution. After completion of the reaction, (monitored through TLC) the reaction mixture was quenched with ice cold water and extracted into chloroform (2x50 mL).The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to yield the crude product which was purified by column chromatography using a mixture of ethyl acetate and hexane as an eluent(10:90 for product **2**and25:75for product **3**).

Typical procedure for the synthesis of3-Ethylidene/Isopropylidene-2-aryl-2,3-dihydro-1*H*-quinolin-4-ones 2a-h: To a well stirred solution of *trans*-3-vinyl/isopropenyl-*β*-lactam **1**(30 mmol) in dry chloroform (20 mL) was added a solution of triflic acid(10 mmol) and the reaction mixture was refluxed for 3 hrs.After completion of the reaction, (as evidenced *via* TLC) the reaction mixture was quenched withice cold water and extracted into chloroform (2x50 mL).The combined organic layers were dried over anhydrous Na_2SO_4,concentrated under vacuoand purified by column chromatography using a mixture (10:90) of ethyl acetate and hexane as an eluent to yield desired product **2.**

Typical procedure for the synthesis of 3-ethylidene-6-methyl-2-phenyl-2,3-dihydro-1H-quinolin-4-one 2a in the presence of base: To a well stirred mixture of **2a** and **3a** in dry chloroform was added triethylamine and the reaction was stirred for 12 hrs at room temperature. After the completion of the reaction (as evidenced *via* TLC), the reaction mixture was extracted into chloroform (2x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under vacuo to yield the product **2a,** which was purified *via* column chromatography using a mixture of ethyl acetate and hexane (10:90) as an eluent.

3-ethylidene-6-methyl-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one(2a): White solid; m.p.118-119 °C;^{1}H NMR (300MHz, $CDCl_3$): δ :1.47 (d, J = 7.5 Hz, 3H, -CH_3), 1.66 (s, 1H, H^2), 2.31 (s, 3H, -CH_3), 3.89 (q, J = 7.5 Hz, 1H, H^4), 7.10-7.52 (m, 8H, ArH), 7.69 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ :16.1, 20.8, 44.8, 120.0, 122.9, 123.1, 127.0, 127.3, 129.5, 133.9, 134.0, 135.3, 141.0, 147.1, 150.3, 162.8; ESI-MS $[M + H]^+$ m/z264; Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32Found: C, 82.19, H, 6.64, N, 5.25.

6-methyl-2-phenyl-3-vinyl-2,3-dihydro-1*H*-quinolin-4-one(3a):Yellow liquid; ^{1}H NMR (300MHz, $CDCl_3$): δ : 2.23 (s, 3H, -CH_3), 3.50 (t, J = 6.2 Hz, 1H, H^3), 4.12 (d, J = 6.0 Hz, 1H, H^2), 5.12-5.21 (m, 2H, H^5), 5.73-5.82 (m, 1H, H^4), 6.72-7.22 (m, 8H, ArH), 8.28 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ: 20.8, 48.1, 52.8, 115.3, 118.6, 124.8, 127.0, 127.7, 128.6, 128.8, 129.9, 133.1, 133.8, 133.9, 141.3, 170.4;ESI-MS [M + H]$^+$ m/z264; Anal. Calcd for$C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32Found: C, 82.21, H, 6.42, N, 5.43.

3-ethylidene-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (2b):White solid; m.p.119-120 °C;^{1}H NMR (300MHz, $CDCl_3$): δ: 1.49 (d, J = 7.5 Hz, 3H, -CH_3), 1.62 (s, 1H, H^2), 3.91 (q, J = 7.2 Hz, 1H, H^4), 7.10-7.60 (m, 9H, ArH), 7.70 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ : 16.1, 44.8, 119.8, 122.9, 123.2, 124.3, 127.0, 127.3, 129.0, 134.2, 137.9, 140.9, 146.9, 150.3, 163.0;ESI-MS [M + H]$^+$ m/z250;Anal. Calcd for$C_{17}H_{15}NO$:C, 81.90; H, 6.06; N, 5.62. Found: C, 81.98; H, 6.19, N, 5.54.

2-phenyl-3-vinyl-2,3-dihydro-1*H*-quinolin-4-one (3b):Yellow liquid; ^{1}H NMR (300MHz, $CDCl_3$): δ : 3.53 (t, J = 6.0 Hz, 1H, H^3), 4.17 (d, J = 5.7 Hz, 1H, H^2), 5.10-5.21 (m, 2H, H^5), 5.72-5.84 (m, 1H, H^4), 6.80 (m, 1H, ArH), 7.00 (d, J = 7.2 Hz, 2H, ArH), 7.12 (d, J = 7.2 Hz, 2H, ArH), 7.20-7.37 (m, 4H, ArH), 8.23 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ :48.2, 52.8, 115.6, 118.3, 123.5, 125.1, 127.1, 127.7, 128.2, 128.8, 129.3, 133.7, 136.4, 141.1, 170.8;ESI-MS [M + H]$^+$ m/z250;Anal. Calcd for$C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62.Found: C, 81.84, H, 6.16, N, 5.71.

6-chloro-3-ethylidene-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (2c): White solid;m.p.121-122 °C;^{1}H NMR (300MHz, $CDCl_3$): δ :1.47 (d, J = 7.2 Hz, 3H, -CH_3), 1.64 (s, 1H, H^2), 3.93 (q, J = 7.5 Hz, 1H, H^4), 6.90-7.52 (m, 8H, ArH), 7.72 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ :16.2, 44.3, 119.6, 122.7, 123.1, 124.4, 127.0, 127.5, 129.2, 134.4, 137.8, 140.7, 146.5, 150.2, 163.1;ESI-MS [M + H]$^+$ m/z284, [M + H]$^{2+}$ m/z285; Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94Found: C, 71.78, H, 4.82, N, 4.80.

6-chloro-2-phenyl-3-vinyl-2,3-dihydro-1*H*-quinolin-4-one (3c): Yellow liquid;^{1}H NMR (300MHz, $CDCl_3$): δ : 3.55 (t, J = 5.7 Hz, 1H, H^3), 4.19 (d, J = 6.0 Hz, 1H, H^2), 5.12-5.24 (m, 2H, H^5), 5.70-5.82 (m, 1H, H^4), 6.83 (m, 1H, ArH), 7.05 (d, J = 7.5 Hz, 2H, ArH), 7.10 (d, J = 7.2 Hz, 2H, ArH), 7.22-7.40 (m, 3H, ArH), 8.21 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ :48.4, 52.7, 115.5, 118.6, 123.4, 125.2, 127.4, 127.7, 128.3, 128.9, 129.2, 133.6, 136.3, 141.2, 170.7 ppm.ESI-MS [M + H]$^+$ m/z284, [M + H]$^{2+}$ m/z285;Anal. Calcd for$C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.82, H, 4.85, N, 4.83.

3-ethylidene-6-methyl-2-*p*-tolyl-2,3-dihydro-1*H*-quinolin-4-one (2d):White solid; m.p.123-124 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ :1.48 (d, J = 7.2 Hz, 3H, -CH_3), 1.68 (s, 1H, H^2), 2.32 (s, 3H, -CH_3), 2.34 (s, 3H, -CH_3), 3.94 (q, J = 7.2 Hz, 1H, H^4), 7.08 (d, J = 7.2 Hz, 2H, ArH), 7.15 (d, J = 7.2 Hz, 2H, ArH), 7.22-7.47 (m, 3H, ArH), 7.76 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ= 16.4, 20.4, 20.6, 44.5, 119.6, 122.5, 123.7, 124.1, 127.5, 127.6, 129.3, 134.4, 137.5, 140.7, 146.4, 150.8, 163.2 ppm.ESI-MS [M + H]$^+$ m/z278; Anal. Calcd for$C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.12, H, 6.74, N, 5.25.

6-methyl-2-*p*-tolyl-3-vinyl-2,3-dihydro-1*H*-quinolin-4-one (3d): Yellow liquid; ^{1}H NMR (300MHz, $CDCl_3$): δ :2.31 (s, 3H, -CH_3), 2.34 (s, 3H, -CH_3), 3.53 (t, J = 6.0 Hz, 1H, H^3), 4.19 (d, J = 6.0 Hz, 1H, H^2), 5.17-5.27 (m, 2H, H^5), 5.70-5.82 (m, 1H, H^4), 7.11 (d, J = 7.2 Hz, 2H, ArH), 7.17 (d, J = 7.2 Hz, 2H, ArH), 7.24-7.49 (m, 3H, ArH), 8.24 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ : 20.3, 20.7, 48.1, 52.7, 115.6, 118.1, 123.7, 125.2, 127.6, 127.9, 128.1, 128.5, 129.2, 133.6, 136.8, 141.4, 170.6;ESI-MS [M + H]$^+$ m/z278;Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05.Found: C, 82.37, H, 6.72, N, 5.17.

3-isopropylidene-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (2e):White solid;m.p.115-116 °C;^{1}H NMR (300MHz, $CDCl_3$): δ = 1.36 (s, 1H, H^2), 2.06 (s, 3H, -CH_3), 2.27 (s, 3H, -CH_3), 6.74-7.29 (m, 9H, ArH), 7.73 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ= 22.5, 23.5, 46.2, 114.9, 117.1, 122.7, 124.7, 125.9, 126.7, 127.7, 128.9, 129.2, 136.3, 141.5, 147.2, 165.9; ESI-MS [M + H]$^+$ m/z264; Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.23, H, 6.39, N, 5.52.

3-isopropenyl-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (3e):Yellow liquid; ^{1}H NMR (300MHz, $CDCl_3$): δ :2.05 (s,3H,-CH_3), 5.64 (s, 1H, H^{4a}), 5.74 (s, 1H, H^{4b}), 6.66 (d, J= 6.0Hz, 1H, H^3), 6.71 (t, J= 3.0, 6.0 Hz, 1H, H^2), 7.11-7.55 (m, 9H, ArH), 7.86 (d, J= 3.0 Hz, NH, exchangeable with D_2O); ^{13}C NMR (75MHz, $CDCl_3$):δ: 19.8, 50.0, 57.9, 114.8, 117.4, 120.4, 125.6, 127.4, 128.0, 128.6, 129.6, 134.6, 141.8, 147.4, 148.7, 185.8;ESI-MS [M + H]$^+$ m/z264; Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.21, H, 6.65, N, 5.24.

6-chloro-3-isopropylidene-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (2f):White solid; m.p.124-125 °C;^{1}H NMR (300MHz, $CDCl_3$): δ :1.69 (s, 6H, -CH_3), 2.64 (t, J= 2.4Hz, 1H, H^2), 3.71 (d, J= 2.2 Hz, NH, exchangeable with D_2O), 7.17-7.56 (m, 8H, ArH);^{13}C NMR (75MHz, $CDCl_3$):δ=16.2, 16.4, 44.3, 119.2, 122.4, 123.1, 124.6, 127.2, 127.5, 129.4, 134.2, 137.5, 140.6, 146.2, 150.4, 163.6;ESI-MS [M + H]$^+$ m/z298;[M + H]$^{2+}$ m/z299.Anal. Calcd for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70. Found: C, 72.45, H, 5.54, N, 4.58.

6-chloro-3-isopropenyl-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (3f):Yellow liquid;^{1}H NMR (300MHz, $CDCl_3$): δ :2.02 (s,3H,-CH_3), 5.61 (s, 1H, H^{4a}), 5.73 (s, 1H, H^{4b}), 6.62 (d, J= 6.0Hz, 1H, H^3), 6.70 (t, J= 3.3, 6.0 Hz, 1H, H^2), 7.05-7.45 (m, 8H, ArH), 7.81 (d, J= 3.3 Hz, NH, exchangeable with D_2O); ^{13}C NMR (75MHz, $CDCl_3$):δ : 20.1, 50.3, 57.6, 114.9, 117.2, 120.6, 125.8, 127.3, 128.0, 128.7, 129.5, 134.8, 141.9, 147.5, 148.8, 185.1; ESI-MS [M + H]$^+$ m/z298, [M + H]$^{2+}$ m/z299; Anal. Calcd for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70. Found: C, 72.71, H, 5.56, N, 4.82.

3-isopropylidene-6-methyl-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (2g): White solid;m.p.127-128 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ :1.48 (s, 1H, H^2), 2.02 (s, 3H, -CH_3), 2.16 (s, 3H, -CH_3), 2.30 (s, 3H,-CH_3), 7.08-7.42 (m, 8H, ArH), 7.79 (s, 1H, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ : 19.2, 22.1, 23.5, 46.2, 114.5, 117.1, 122.6, 124.6, 125.9, 126.7, 127.6, 128.7, 129.3, 136.1, 141.6, 147.5, 165.8;ESI-MS [M + H]$^+$ m/z278;Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.12, H, 6.74, N, 5.21.

3-isopropenyl-6-methyl-2-phenyl-2,3-dihydro-1*H*-quinolin-4-one (3g): Yellow liquid;^{1}H NMR (300MHz, $CDCl_3$): δ :2.07 (s,3H,-CH_3), 2.31 (s, 3H,-CH_3), 5.62 (s, 1H, H^{4a}), 5.70 (s, 1H, H^{4b}), 6.68 (d, J= 6.3 Hz, 1H, H^3), 6.75 (t, J= 3.0, 6.3 Hz, 1H, H^2), 7.10-7.59 (m, 8H, ArH), 7.88 (d, J= 3.0 Hz, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ= 19.6, 20.4, 50.2, 57.5, 114.6, 117.6, 120.8, 125.9, 127.4, 128.2, 128.9, 129.6, 134.7, 141.8, 147.6, 148.8, 185.7;ESI-MS [M + H]$^+$ m/z278; Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.41, H, 6.77, N, 5.18.

3-isopropylidene-6-methyl-2-*p*-tolyl-2,3-dihydro-1*H*-quinolin-4-one (2h):White solid; m.p.114-115 °C; ^{1}H NMR

(300MHz, $CDCl_3$): δ: 1.41 (s, 1H, H^2), 2.00 (s, 3H, -CH_3), 2.14 (s, 3H, -CH_3), 2.31 (s, 3H,-CH_3), 2.36 (s, 3H,-CH_3), 7.00-7.42 (m, 7H, ArH), 7.82 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75MHz, $CDCl_3$):δ : 19.4, 19.7, 22.3, 23.6, 46.4, 114.7, 117.2, 122.5, 124.3, 125.8, 126.5, 127.8, 128.9, 129.4, 136.2, 141.4, 147.8, 165.9;ESI-MS $[M + H]^+$ m/z292; Anal. Calcd for$C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.31, H, 7.37, N, 4.65.

3-isopropenyl-6-methyl-2-*p*-tolyl-2,3-dihydro-1*H*-quinolin-4-one (3h):Yellow liquid;^{1}H NMR (300MHz, $CDCl_3$): δ:2.04 (s, 3H, -CH_3), 2.27 (s, 3H,-CH_3), 2.33 (s, 3H,-CH_3), 5.60 (s, 1H, H^{4a}), 5.72 (s, 1H, H^{4b}), 6.65 (d, *J*= 6.6 Hz, 1H, H^3), 6.72 (t, *J*= 3.0, 6.6 Hz, 1H, H^2), 7.00-7.52 (m, 7H, ArH), 7.89 (d, *J*= 3.0 Hz, NH, exchangeable with D_2O);^{13}C NMR (75MHz, $CDCl_3$):δ : 19.8, 20.2, 20.3, 50.6, 57.8, 114.6, 117.9, 120.1, 125.8, 127.3, 128.1, 128.7, 129.5, 134.6, 141.9, 147.4, 148.5, 185.6 ppm.ESI-MS $[M + H]^+$ m/z292; sAnal. Calcd for$C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.56, H, 7.16, N, 4.95.

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Notes and references

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