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[Et_3NH][HSO_4]-mediated functionalization of hippuric acid: an unprecedented approach to 4-arylidene-2-phenyl-5(4*H*)-oxazolones

Mehtab Parveen,*[a] Faheem Ahmad,[a] Ali Mohammed Malla,[a] Shaista Azaz,[a] Manuela Ramos Silva[b] and P. S. Pereira Silva[b]

[a]*Division of Organic Synthesis, Aligarh Muslim University, Aligarh, 202002, India*

[b]*CEMDRX Physics Department, University of Coimbra, 3004-516 Coimbra, Portugal*

Abstract

A facile, green and stereoselective approach for the synthesis of azlactones/oxazolone **3**(**a-q**) has been developed. The protocol involves reaction of hippuric acid and substituted heterocyclic/aromatic aldehydes in ionic liquid [Et_3NH][HSO_4] to yield desired 4-arylidene-2-phenyl-5(4*H*)-oxazolones in excellent yields (94-97%) with high degree of purity. The remarkable feature of this pathway is that the ionic liquid eliminates the use of toxic and expensive acetic anhydride and is endowed with catalytic and medium engineering ability. This eco-friendly approach improved synthetic efficiency (94-97% yield), minimizing the production of chemical wastes without using highly toxic reagents for the synthesis and more notably, it promoted the selectivity for *Z*-azlactones/oxazolones. Density functional theory (DFT) calculations revealed that the *Z*-isomer of compound **3a** is stabilised by 2.32 kcal mol^{-1} more than the *E*-isomer. This synthetic scheme possesses diverse applicability and is compatible to a range of functional groups (electron donating/ electron withdrawing).

Keywords: Eco-friendly, Solvent-free, Azlactones/oxazolones, [Et_3NH][HSO_4], DFT studies, X-ray analysis, Stereoslectivity

**Corresponding author: Mehtab Parveen*
E-mail: mehtab.organic2009@gmail.com; Tel: +91-9897179498

Introduction

The first synthesis of Erlenmeyer azlactones, 4-Arylidene-2-phenyl-5(4*H*)-oxazolones has been reported by Friedrich Gustav Carl Emil Erlenmeyer way back in 1893,[1] representing an important class of five-membered heterocyclic motifs possessing nitrogen and oxygen as hetero atoms in their structural framework. The literatures revealed that C-2 and C-4 positions of the azlactones are significant for their various biological activities.[2] Azlactones have been found to be promising intermediates for the synthesis of variety of organic motifs, including *N*-substituted pyrroles,[3] amino acids,[4] α-acylaminoalcohols ,[5] thiamine,[6] amides,[7] peptides[8] and other heterocyclic precursors.[9] They have been also used as synthons for the construction of various alkaloid skeletons,[10] immunomodulators[11] and biosensors coupling and/or photosensitive composition devices for proteins.[12] Recently, Zimmermann *et al.*[13] have reported the application of azlactones for the synthesis of methacrylamidopeptide macromonomers, employed in the synthesis of hydrogel supports for *in-vivo* cell growth. Moreover, a plethora of medicinally important compounds bearing azlactones in their structural framework have been reported possessing antimicrobial,[14] antitumor,[15] antioxidant,[16] anti-inflammatory,[17] anti-HIV,[18] anticonvulsant,[19] antihypertensive[20] and tyrosinase inhibitors[21] useful for the treatment of skin diseases associated with melanin hyperpigmentation (Fig. 1). They have also been used in active site titrations of enzymes.[22] Such immense synthetic utility and inherent pharmacological applications of azlactones have inspired the organic chemists to develop various efficient and elegant protocols for their synthesis.

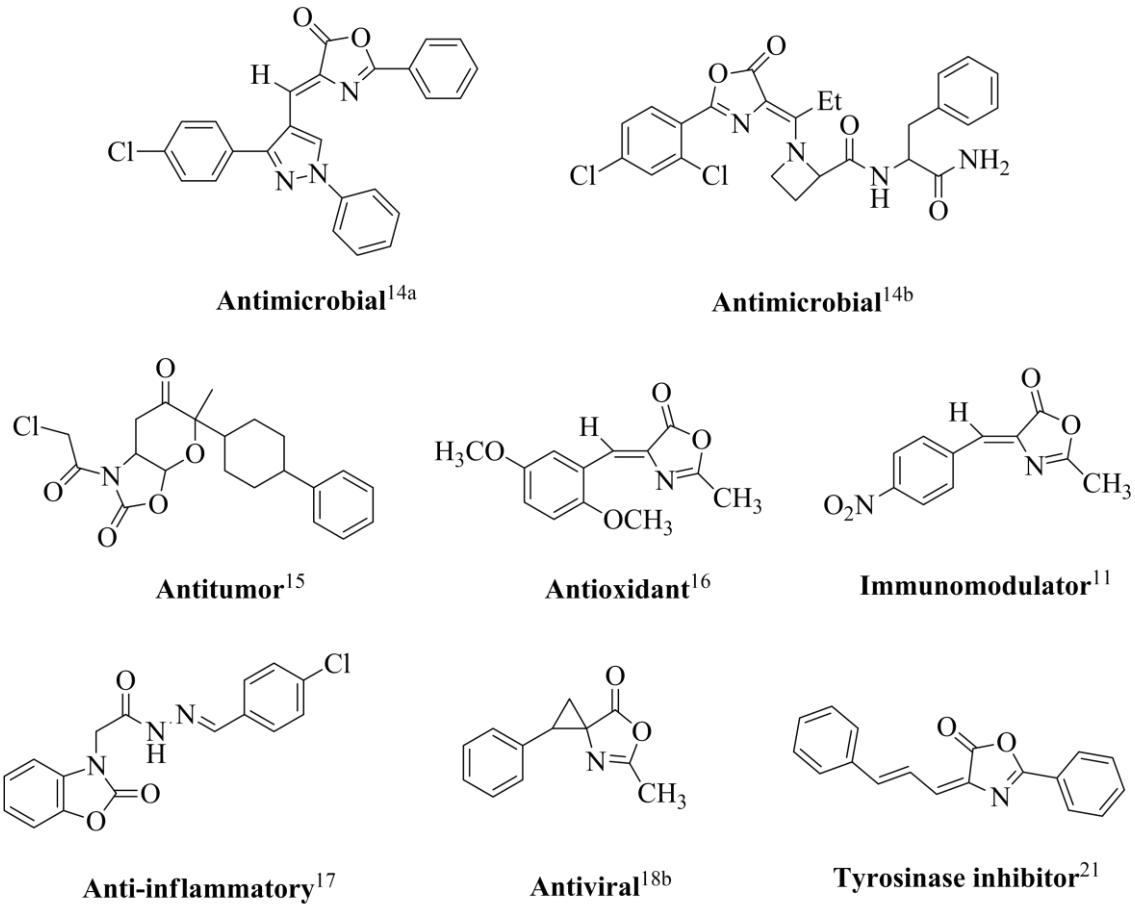


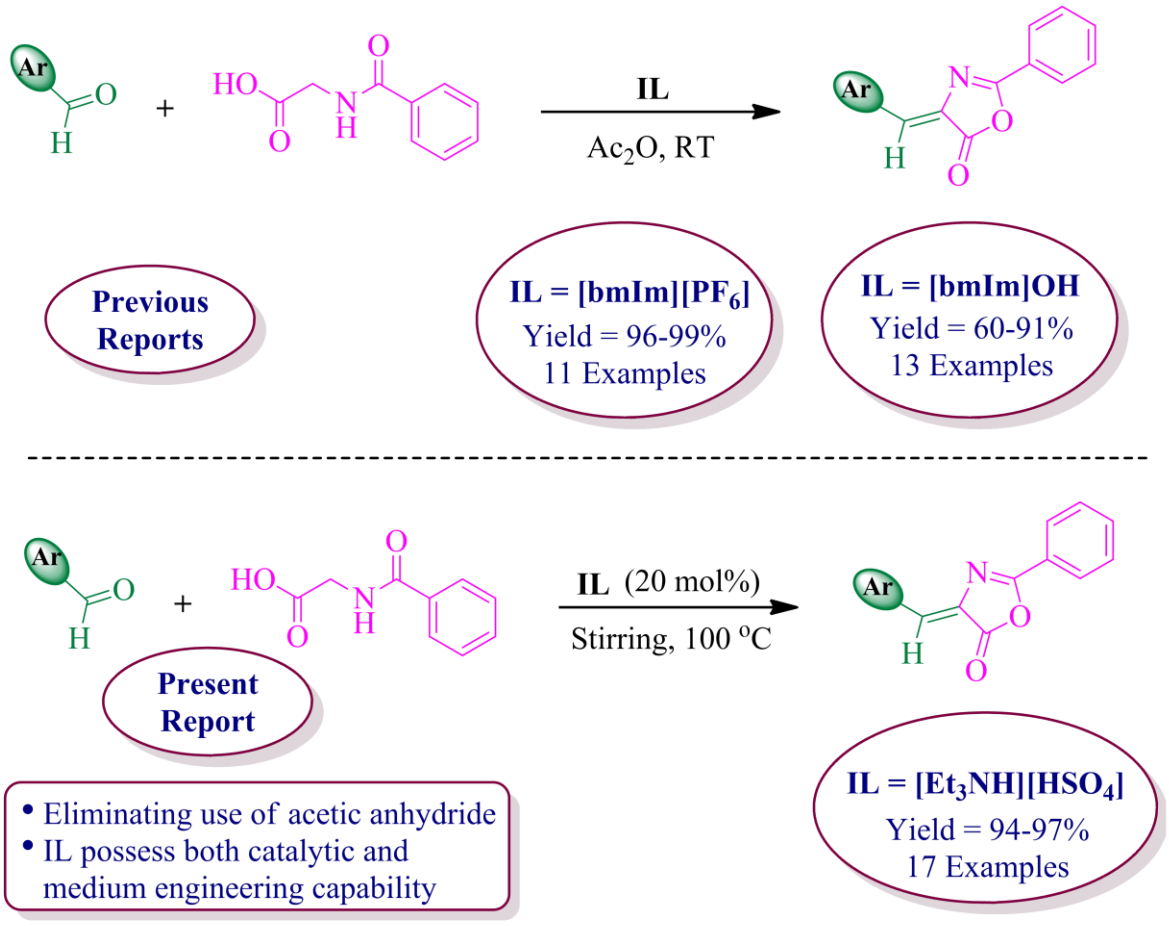
Figure 1 Biologically active molecules bearing oxazolone moiety in their structural framework

The most well-known method for synthesis of azlactone is Erlenmeyer method, which involves the direct condensation of aryl aldehydes with hippuric acid in the presence of acetic anhydride as dehydrating agent and anhydrous sodium acetate as a homogeneous basic catalyst.[23] The catalyst promoted synthesis has become one of the hot areas in organic synthesis in the last few decades. At present, a wide range of methods for synthesizing azlactones in the presence of catalyst are available *viz*. $POCl_3$,[24] carbodiimides,[25] polyphosphoric acid,[26] perchloric acid[27] and SO_3 in DMF.[28] In a spam of last nineteen years

i.e. 1994-2013 several syntetic routes have been developed for the synthesis of azlactones using different catalysts such as Al_2O_3,[29] $Bi(OAc)_3$,[30] $Bi(OTf)_3$,[31] silica-supported heteropolyacids,[32] $Yb(OTf)_3$,[33] $Ca(OAc)_2$,[34] supported KF,[35] anhydrous $ZnCl_2$,[36] Fe_2O_3,[37] ZnO[38] and Al_2O_3-H_3BO_3.[39] Although, all of these reported protocols have certain merits, still numbers of them have suffered from several shortcomings including use of expensive and hazardous reagents, application of high boiling solvents, prolonged reaction times, tedious workup procedures, high temperature, toxic waste generation, difficulty in separation and recovery of the catalyst. Hence, it is of great practical importance to develop more versatile, simple and environmentally benign methodologies, which will avoids or minimize all of these complications.

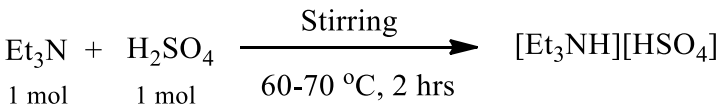
In recent years, new safety and environmental requirements have motivated a great deal of interest for organic chemists towards the design of new reaction systems satisfying the green chemistry principles. Classical methods are being rectified to replace the profusely used toxic volatile organic solvents (VOS) by suitable alternate solvent systems for easy chemical transformations with the minimum generation of hazardous chemical wastes and environmental pollution.[40] Among the different strategies for accomplishing this goal, ionic liquids (ILs) have attracted significant research interest due to their unique physicochemical properties and environment friendly nature.[41] From the past few decades ionic liquids due to their exceptional features such as an almost undetectable vapour pressure, high thermal and chemical stability, non-explosive properties, controlled miscibility, potentially recyclable properties and strong solvent power for a wide range of organic, inorganic, and polymeric molecules have attracted considerable attention as environmentally benign reaction media in the green organic synthesis.[42-48] Moreover, ionic liquids are called ‘‘designer solvents’’ and have been proved to be very excellent catalysts as well as solvents for various organic transformations.[49-51]

Till now, only few ionic liquids such as [bmim][BF_4][52] and [bmim][OH][53] have been reported for the synthesis of azlactones (Scheme 1). Since the utility of imidazolium ionic liquids in the organic synthesis has been proven as the better alternative reaction media and catalyst but the difficulty in preparation, their expensive cost and high toxicity confine their applicability in synthetic transformations.[54] This led the organic chemist to explore alternative greener, milder, cheaper and efficient ILs in organic synthesis. In this regard ammonium ionic liquid offers promising substitute due to their fascinating features such as low cost, eco-friendly nature, facile synthesis, ease in separation, reusability and stability towards water and air.[55]



Scheme 1 Synthetic route for azlactone synthesis employing IL

Motivated by these findings, and in continuation of our on-going interest endowed with the finding of novel synthetic protocols[56] under the principles of green chemistry, herein, we report a convenient and expeditious protocol for the synthesis of Erlenmeyer azlactones from hippuric acid and aldehydes in the presence of Bronsted acid ionic liquid $[Et_3NH][HSO_4]$ as a green, efficient, cheap and recyclable catalyst as well as solvent. To the best of our knowledge, $[Et_3NH][HSO_4]$ has yet not been explored so far for the synthesis of azlactones. The ionic liquid $[Et_3NH][HSO_4]$ has been prepared by employing standard procedures depicted in the literature (Scheme 2).[57] It has emerged as a promising catalyst in many organic transformations[58] and possesses environmentally benign properties such as nontoxicity, biocompatibility, recyclability, inexpensiveness and thermal stability. The proficiency of this ionic liquid as both catalyst and medium made this protocol more practical than the already reported procedures as it eliminates the use of toxic and expensive acetic anhydride. Besides this, our present approach also displays some specific advantages as it gives excellent yield (%) within a minimum reaction time and can tolerate a wide range of functional groups. The structure of the model compound **3a** has been authenticated on the basis of single-crystal X-ray analysis and density functional theory (DFT) calculations.



Scheme 2 Pathway for the synthesis of ionic liquid

Results and Discussion

In the present study a library of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (Erlenmeyer azlactones) derivatives **3** (**a**-**q**) have been synthesized by using environmentally benign ionic

liquid [Et_3NH][HSO_4] possessing both catalytic as well as medium engineering capability. This protocol offers several advantages over other existing synthetic methodologies in terms of yield (94-97 %), purity of products, reaction times, operational procedure, catalyst stability and recyclability. This synthetic scheme possesses diverse applicability and is compatible to a range of functional groups (electron donating/ electron withdrawing).

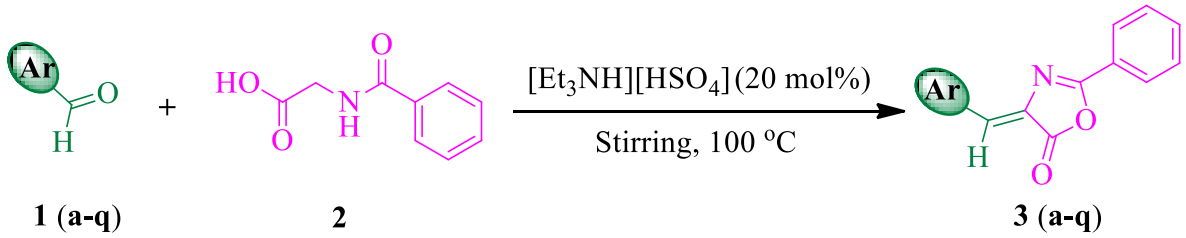
Characterization of [Et_3NH][HSO_4] ionic liquid

The synthetic route for the preparation of the catalyst (IL) employed in the present protocol has been shown in Scheme 2. The ionic liquid [Et_3NH][HSO_4] obtained has been characterized on the basis of ^{1}H NMR and ^{13}C NMR spectral analysis. In the ^{1}H NMR spectrum, a triplet resonating at around δ 1.32 integrating for nine protons signifies the presence of three methyl (3 × CH_3) group. Similarly, a multiplet resonating at δ 3.25 has been attributed to six protons of methylene (3 × CH_2) group. A sharp singlet at δ 9.08 for one proton has been assigned to -NH (D_2O-exchangeable) proton (Fig. S1†). In ^{13}C NMR spectral study, a pair of strong absorption band resonating at around δ 16.27 and 59.35 has been assigned to methyl (CH_3) and methylene (CH_2) carbons, respectively (Fig. S2†). The spectral data was found to be in good agreement, thus confirmed the formation of desired ionic liquid [Et_3NH][HSO_4].

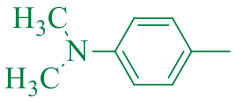
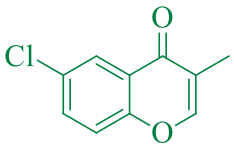
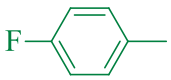
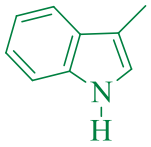
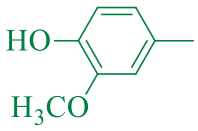
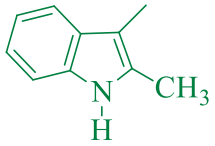
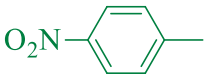
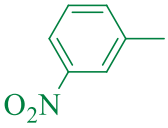
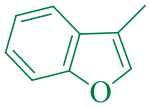
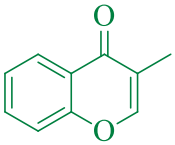
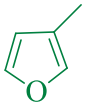
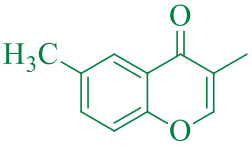
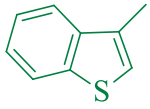
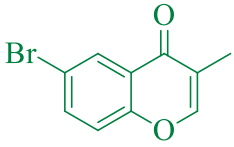
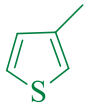
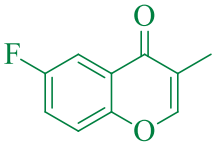
Chemistry

The synthetic pathway for the preparation of series of azlactones/oxazolone **3** (**a**-**q**) has been depicted in Scheme 3. Herein, a series of compounds were typically accessed *via* a solvent free, efficient and environmentally benevolent cyclodehydration-condensation reaction process, involving various heterocyclic/aromatic aldehydes with hippuric acid in the presence of IL [Et_3NH][HSO_4] to yield target 4-arylidene-2-phenyl-5(4*H*)-oxazolones in excellent

yields (94-97 %) with high degree of purity. The structural elucidation of all the synthesized compounds **3** (**a**-**q**) has been established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. The analytical results for C, H and N were found to be within ± 0.3% of the theoretical values. The spectral analysis has been in good corroboration with the expected structural framework of the synthesized compounds. IR spectrum of all the synthesized compounds displayed characteristic signals for (-C=N), lactone carbonyl (C=O) and (CO-O) resonating at around 1638-1656, 1745-1764 and 1192-1215 cm^{-1}, respectively. The exocyclic double bond attached to the oxazolone ring displayed the absorption band resonating around 1594-1624 cm^{-1}. Characteristic peaks for the different substituted functional moieties such as nitro, methoxy and C=O$_{\gamma\text{-}pyrone}$ etc., have been discussed in the experimental section. In ^{1}H NMR spectral analysis, each synthesized compound exhibited a characteristic sharp down field singlet resonating at around δ 7.32-7.44, attributed to the olefinic (=C-H) proton which is in agreement with the *Z*-configuration as reported in the literature.[59] The aromatic protons of the phenyl ring attached at the position 2 of azlactones ring were exhibited a multiplet resonating in the range of δ 7.50-8.10. In ^{13}C NMR spectral study, the absorption band resonating at around δ 170.0-175.3 has been assigned to the carbonyl group of the azlactone ring. Similarly, the signals at δ 132.5-135.5, 136.4-143.2 and 159.7-163.8 has been attributed to vinylic, C-4 and C-2 carbon of the products, respectively. The detailed spectral assignment of the compound **3** (**a**-**q**) has been discussed in experimental section. The mass spectral analysis of all the synthesized azlactone derivatives has been found to be in good conformity with the proposed structures. The molecular structure of compound **3a** was further supported by single crystal X-ray crystallographic analysis.



1 (a-q) **2** **3 (a-q)**

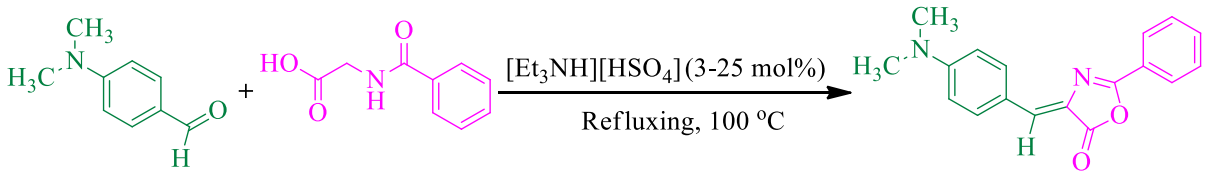
Products	Ar	Products	Ar
3a		**3j**	
3b		**3k**	
3c		**3l**	
3d		**3m**	
3e		**3n**	
3f		**3o**	
3g		**3p**	
3h		**3q**	
3i			

Scheme 3 Synthetic scheme for the synthesis of azlactone derivatives **3** (**a-q**)

Optimization of reaction condition

Initially, we focused our study to probe the optimized reaction conditions for the present protocol including amount of catalyst, reaction temperature and investigating efficiency of various catalyst on a selected model reaction using *p*-(*N*,*N*-dimethylamino)benzaldehyde **1a** and hippuric acid **2** to establish the best possible reaction conditions for the synthesis of azlactone **3a**. In order to optimize the reaction conditions we first probed the effect of the catalyst loading by carrying out the model reaction with different concentration of the catalyst *viz*. 3, 5, 10, 15, 20 and 25 mol% at 100 ^{o}C under solvent free condition and the results were noted in terms of reaction time and yield (Table 1). The results revealed that with every subsequent increase in concentration of catalyst from 3 mol% to 20 mol%, there has been a remarkable improvement in the yield from 55-97 %, with prominent drop in reaction time from 140-15 mins (entries 1-5, Table 1). However, further increase in the concentration of the catalyst (>20 mol%) did not have any significant effect on the reaction. It can be inferred from the above results (entry 5, Table 1) that 20 mol% of the catalyst is satisfactory to gain the optimum yield in the shortest reaction time under neat conditions at 100 ^{o}C, therefore 20 mol% of the catalyst was selected for further studies.

Table 1 Effect of catalyst loading on the model reaction

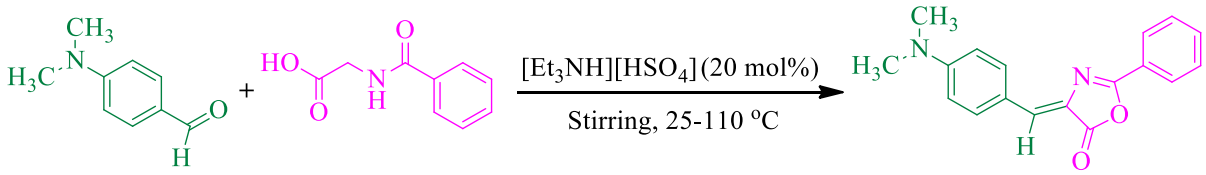


Entry	Catalyst (mol%)	Time (min)[a]	Yield (%)[b]
1	3	140	55
2	5	95	63
3	10	70	73
4	15	45	82
5	20	15	97
6	25	15	97

Reaction conditions: *p*-(*N*,*N*-dimethylamino)benzaldehyde (**1a**, 2 mmol), hippuric acid (**2**, 2 mmol), $[Et_3NH][HSO_4]$ (3-25 mol%), 100 °C.
[a]Reaction Progress monitored by TLC.
[b]Isolated yield of products.

In order to optimize the reaction temperature for the present study we have carried out the model reaction at different temperatures (Table 2). It was noticed that the reaction was strongly influenced by the temperature in terms of yield and reaction time. Initially the reaction was allowed to stir at room temperature it takes almost 5 hrs to complete the reaction with poor yield of the product **3a**. With increase in temperature from 25 to 100 °C, the yield of the desired product **3a** increased significantly from 35-97% within the minimum period of reaction time (entries 1-5, Table 2). However, no further enhancement in the yield of product **3a** was witnessed when the reaction temperature was raised from 100 to 110 °C. Thus, keeping in view the above optimized reaction conditions, 100 °C was chosen as the optimum temperature for all the reactions.

Table 2 Effect of temperature on the model reaction



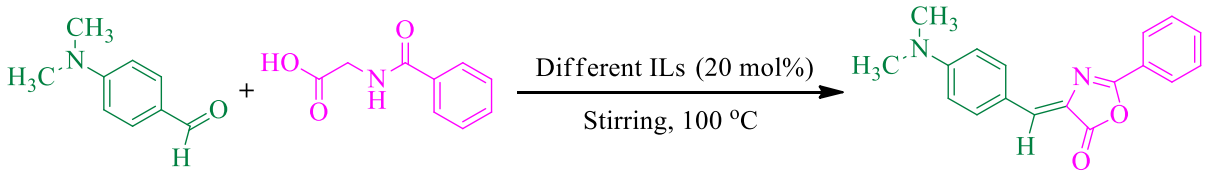
Entry	Temp. (°C)	Time (min)[a]	Yield (%)[b]
1	Room Temp.	5	35
2	50	2	54
3	70	1.5	67
4	90	40	73
5	100	15	97
6	110	15	97

Reaction conditions: *p*-(*N*,*N*-dimethylamino)benzaldehyde (**1a**, 2 mmol), hippuric acid (**2**, 2 mmol), $[Et_3NH][HSO_4]$ (20 mol%), 25-110 °C.
[a]Reaction Progress monitored by TLC.
[b]Isolated yield of products.

In order to establish the superiority of our synthesized ionic liquid $[Et_3NH][HSO_4]$ for the present protocol we have screened different ionic liquids on the model reaction. Table 3 lists the effect of different ionic liquids on the model reaction without using any volatile organic solvents. It was clear from (Table 3) that the catalytic activity was potentially influenced by the anionic part of the ionic liquids. The higher yield of the product was obtained when the strongly acidic $[HSO_4]$ anion was explored (Table 3). However, the reaction was slow and less efficient when the ionic liquids with $[H_2PO_4]$ and $[CH_3COO]$ anions were probed, which may be due to the weaker acidity of the phosphate and acetate anions as compared to $[HSO_4]$ anion. The above results demonstrated that the reaction was strongly influenced by the acidity of the ionic liquids. This can be presumably attributed to the *p*Ka values (acid dissociation constant) of their respective anions (HSO_4, H_2PO_4 and CH_3COO) which offer a quantitative measurement of the strength of an acid, smaller the *p*Ka value, stronger is the acid. The results obtained (Table 3) in terms of products yield and

reaction time are in good agreement with acidity/pKa values of their respective anions which follow the order as: HSO_4 (*p*Ka = -3) > H_2PO_4 (*p*Ka = 2.15) > CH_3COO (*p*Ka = 4). In order to probe the effect of cationic part of the ionic liquid on the azlacones synthesis, the reaction was performed in quaternary ammonium cationic bisulfate ionic liquids with different alkyl chain length. It was found that the cations with shorter alkyl chains gives better yield and the efficiency of the ionic liquids decrease sequentially with the increase in the cation chain length of the ionic liquid (entries 1-3, Table 3). The reason may be that the longer alkyl groups of the ammonium cations lead to bigger aggregations.[60] The cationic ILs with short alkyl chains does not form definite aggregations but those with longer alkyl chains gradually form well-defined aggregations.[61] These aggregations may lead to non-uniform and co-adjacent structure of ILs systems, which causes complication for the transfer of electrons and protons in the molecular interior, thus hindering the reaction which leads to decrease in the yield of the products with stretched reaction times. The similar results were obtained in the case of [HPO_4] and [CH_3COO] that increasing the cationic chain length decreases the yield of the product (entries 4-7, Table 3). These results suggested that the cation part of the ionic liquid influenced the reactivity of ionic liquid to a greater extent. Thus, it is obvious that tuning of triethylammonium cation by HSO_4 anion in the present study provides excellent yields (94-97 %) of the desired products **3a**. These results imply that [Et_3NH][HSO_4] is the best ionic liquid catalyst/promoter for the synthesis of present azlactone derivatives.

Table 3 Effect of ionic liquids on the model reaction



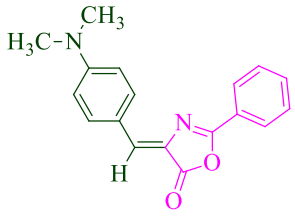
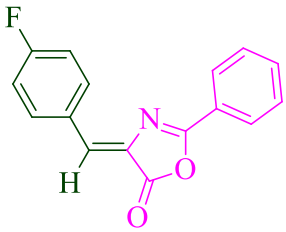
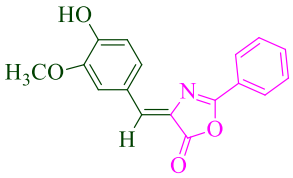
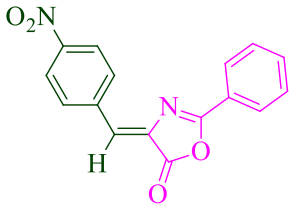
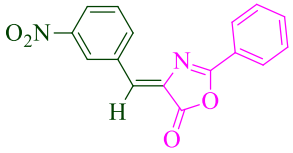
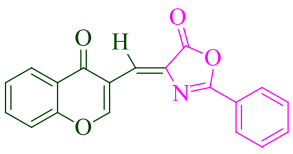
Entry	Catalyst	Time (min)[a]	Yield (%)[b]
1	$[Et_3NH][HSO_4]$	15	97
2	$[Pr_3NH][HSO_4]$	30	90
3	$[Bu_3NH][HSO_4]$	45	84
4	$[Et_3NH][H_2PO_4]$	40	86
5	$[Bu_3NH][H_2PO_4]$	55	68
6	$[Et_3NH][CH_3COO]$	48	78
7	$[Bu_3NH][CH_3COO]$	60	60

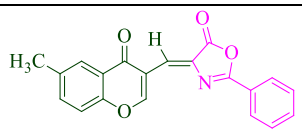
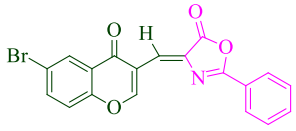
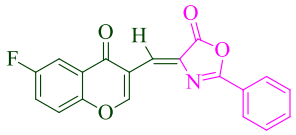
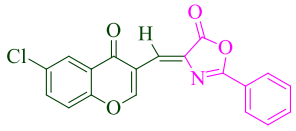
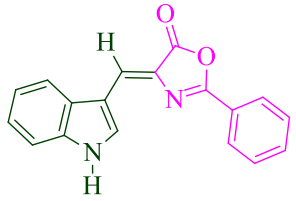
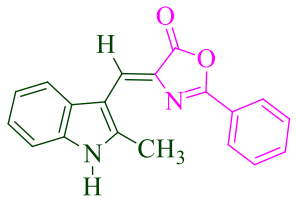
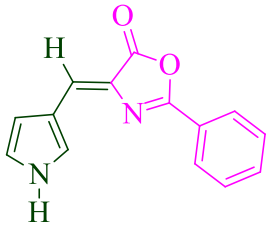
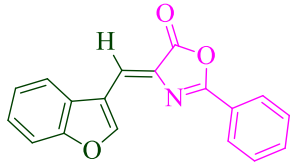
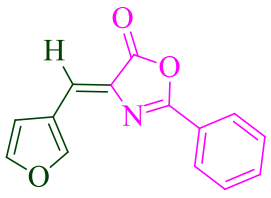
Reaction conditions: *p*-(*N*,*N*-dimethylamino)benzaldehyde (**1a**, 2 mmol), hippuric acid (**2**, 2 mmol), different ionic liquids (20 mol%), 100 °C.
[a]Reaction Progress monitored by TLC.
[b]Isolated yield of products.

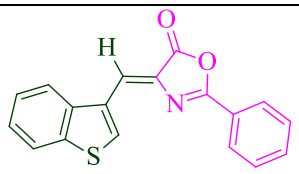
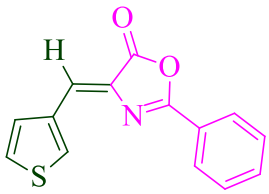
After optimization of the reaction conditions, the substrate scope of $[Et_3NH][HSO_4]$ catalysed system was inspected under the optimized reaction conditions. As shown in Table 4, a wide variety of heterocyclic/aromatic aldehydes possessing electron-withdrawing and electron-donating groups reacted with hippuric acid to afford the corresponding azlactones in excellent yields (94-97%). In the present study a comparative study has also been carried out for the present protocol with the previously reported conventional method by carrying out the reaction of aldehydes with hippuric acid in the presence of acetic anhydride and stoichiometric amounts of sodium acetate. It was observed that the reaction took prolonged reaction time for completion with moderate yield (70-78%). The results revealed that employing ionic liquids $[Et_3NH][HSO_4]$ in the present protocol enhances selectivity and product conversion, thus, proves beneficial over the Erlenmeyer methods for the synthesis of azlactones in terms of yield and reaction times. An important feature of these reactions in

ionic liquids is that there is no evidence for significant formation of a side reaction and the efficient conversion was noticed in the sulfate acid ionic liquids.

Table 4 Synthesis of azlactone derivatives **3** (**a-q**)

Products	Structure	Acetic anhydride[a]		Ionic Liquid[b]	
		Time (hrs)	Yield (%)	Time (min)	Yield (%)
3a		2	78	15	97
3b		2.5	72	18	95
3c		2.5	75	22	94
3d		2.0	70	20	96
3e		2.8	74	23	95
3f		3.0	72	18	96

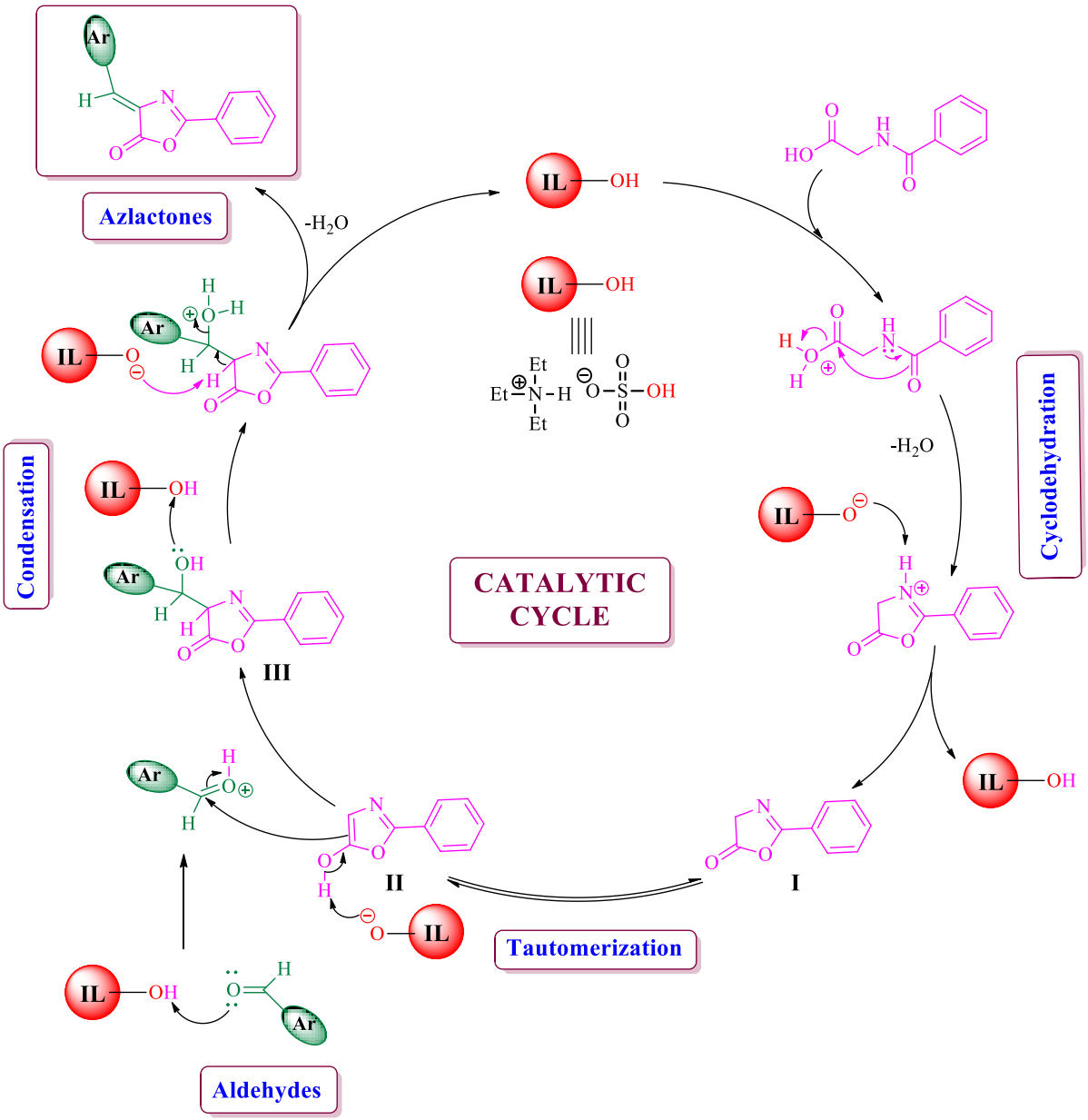
3g		3.2	70	17	97
3h		3.4	74	15	96
3i		3.5	76	24	95
3j		3.0	75	25	96
3k		2.8	73	22	94
3l		3.0	74	18	95
3m		3.2	76	20	97
3n		3.0	71	23	95
3o		3.4	75	19	94

3p		2.8	73	24	96
3q		3.2	76	20	95

[a]*Reaction conditions:* Differently substituted heterocyclic/aromatic aldehydes **1** (**a-q**) (2 mmol) with hippuric acid (**2**, 2 mmol) in presence of acetic anhydride and stoichiometric amounts of sodium acetate at 140 ^{o}C.
[b]*Reaction conditions:* Differently substituted heterocyclic/aromatic aldehydes **1** (**a-q**) (2 mmol) with hippuric acid (**2**, 2 mmol) in $[Et_3NH][HSO_4]$ (20 mol%) at 100 ^{o}C.

Reaction mechanism

The probable mechanistic pathway for the IL $[Et_3NH][HSO_4]$ catalyzed synthesis of azlactone derivatives has been presented in Scheme 4. The reaction is initiated with the protonation of carboxylic group of the hippuric acid by protic ionic liquid $[Et_3NH][HSO_4]$ catalyst which is believed to facilitate the cyclodehydration of the substrate to form intermediate (**I**) which is resonance stabilised as intermediate (**II**). The further protonation of the carbonyl group of the aldehydes by the catalyst generates active electrophilic site for the attack of intermediate (**II**) which facilitates the formation of C-C bond to yield intermediate (**III**). The subsequent elimination of water molecule from intermediate (**III**) promoted by the ionic liquid eventually leads to the formation of target azlactone with the regeneration of the catalyst $[Et_3NH][HSO_4]$.



Scheme 4 Plausible mechanistic catalytic cycle for the synthesis of target azlactone derivatives **3(a-q)**

The stereochemistry around C=C was authenticated by single crystal X-ray crystallographic analysis of compound **3a**, where C=C was found to have *Z*-geometry. Among the two possible geometrical isomers (*E*/*Z*), Z-isomer has been obtained as the exclusive products (Fig. 2), which has been well established further on the basis of density

functional theory (DFT) calculations. This *Z*-selectivity can be interpreted as a way to minimise steric interactions among various substituents. To compare the relative stability of the *E* and *Z*-isomers of the compound **3a**, we have performed the calculation of the vacuum single-point energies of the optimized geometries to obtain the energy differences. It was found that the *Z*-isomer is stabilised by 2.32 kcal mol^{-1} more than the *E*-isomer. This difference in energy is the reason that during crystallization process, *Z*-isomer gets exclusively crystallised out. Moreover, the intramolecular hydrogen bonding between H5 of *N*,*N*-dimethyl phenyl ring and N2 of the azlactone ring enhances its stability which promotes its selectivity than the corresponding *E*-isomer (Fig. 2). The rotations about single bonds (intramolecular torsions) are worth 1-3 kcal mol^{-1} but can be as high as 10 kcal mol^{-1} due to steric factors or restricted rotation,[62] so this can easily explain the calculated energy differences. The agreement between the experimental and calculated geometry has been found to be good (Table 5) and our data suggest that the supramolecular aggregation has little importance in the stabilization of the observed molecular geometry. On the basis of these results, all the synthesized compounds were believed to possess *Z*-configuration across C=C.

Table 5 Comparison of selected geometrical parameters for compound **3a** as determined by X-ray diffraction and from DFT calculation

Torsion angle (^{o})	Form I	Form II (3a)	DFT
C6-C9-C10-N2	0.8(5)	-0.2(4)	-0.09
C7-C6-C9-C10	176.1(3)	-175.1(2)	179.94
N1-C3-C8-C7	179.5(3)	-178.9(2)	-179.52
C12-O1-C11-O2	178.7(3)	-178.3(2)	179.97
N2-C12-C13-C14	-1.5(5)	1.8(4)	-0.13

Note: In a chain of atoms A-B-C-D, a positive torsion angle correspond to a clockwise rotation of the bond A-B in order that it may eclipse the bond C-D and a negative torsion angle requires a rotation in the opposite sense. So, the absolute differences between the torsion angles presented are relatively small.

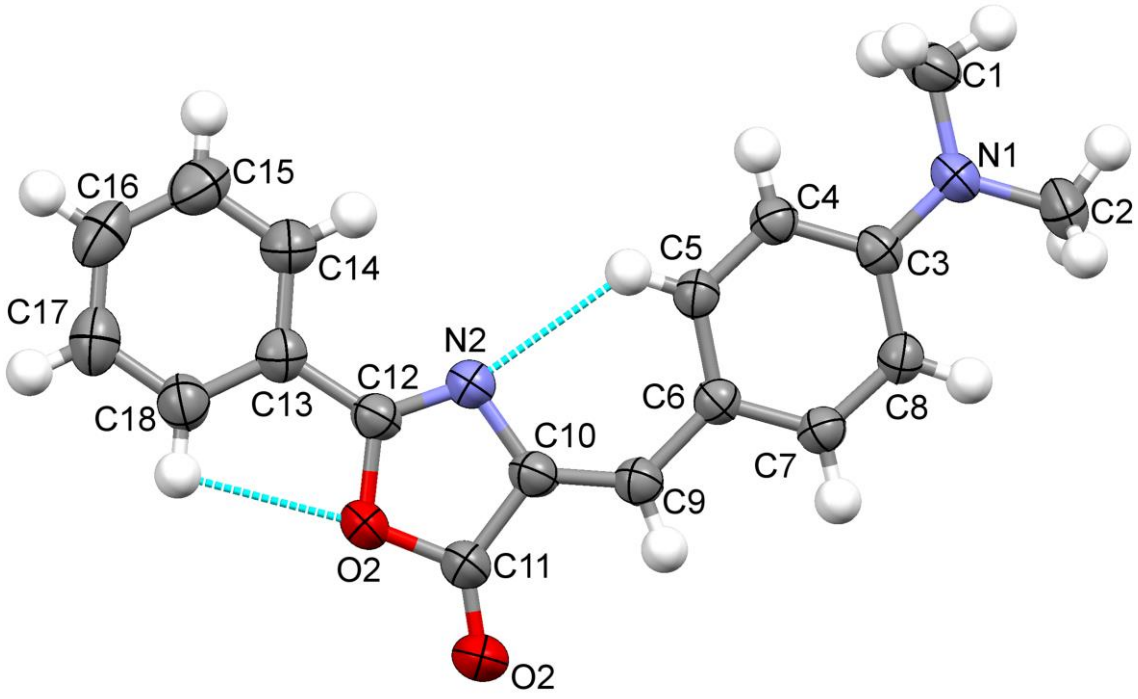


Figure 2 Asymmetric unit of compound **3a** with the ellipsoids drawn at the 50% probability level, with atomic labelling scheme. The intra-molecular interactions are drawn as dashed lines

Recyclability of the catalyst (IL)

The recycling of catalyst is an important step, so as to satisfy the criteria of green chemistry principles and also to manage the cost of the process. In order to explore the extent of recyclability of our catalyst system, the model reaction has been conducted six consecutive times on the same recycled catalyst. After first fresh run with 97% yield, water was added to the reaction mixture and the product was isolated by filtration. The ionic liquid was recovered from the filtrate by removing the water under reduced pressure. The recovered catalyst was then reused for five more subsequent cycles and found to retain its catalytic activity and showed minimal decreases in yield. The product was obtained in 94%, 91%, 88%, 85%, and 83% after successive cycles (Fig. 3) thus, proving the catalyst's reusability with high catalytic

performances. The results demonstrate that our catalytic system is almost stable towards moisture and could be recycled without a significant loss in yield.

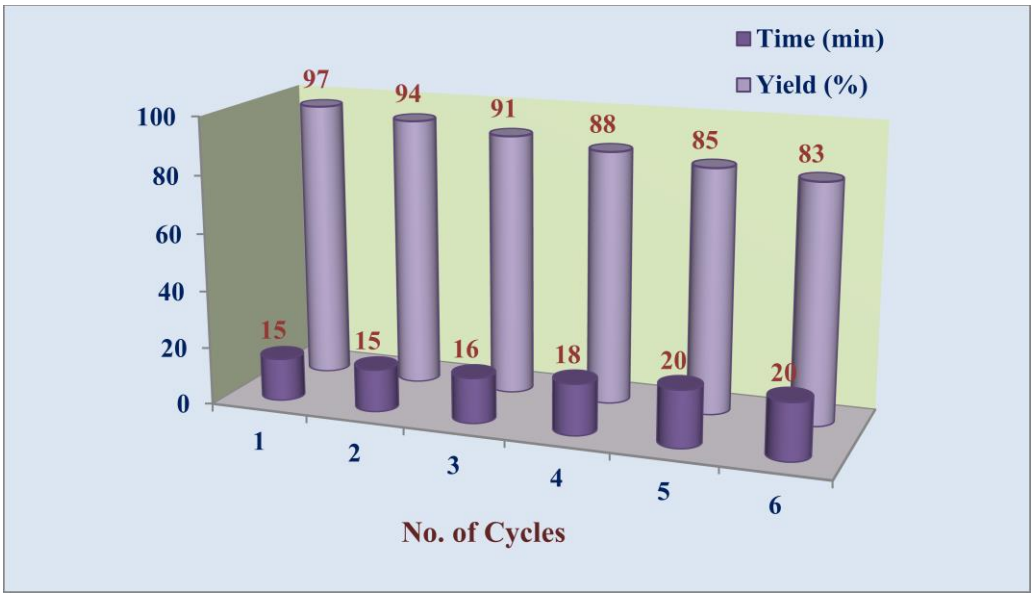


Figure 3 Recyclability of the catalyst

X-ray Crystallographic Study of Compound 3a

In this study we crystalized a new polymorph, form II, of the model compound **3a** (Fig. 2). The unit cell is monoclinic with the non-centrosymmetric and chiral space group $P2_1$. Comparing with the previously published polymorph, form I,[63] our unit cell has similar a, b and β parameters while c parameter with half the value of the reported structure. This led us to suspect that there could be an error in any of the structures. For this reason, several tests were performed to verify the validity of the two structures. The use of the ADSYMM routine in PLATON[64] with the largest tolerances allowed did not reveal any different symmetry for both structures. The simulated powder patterns displayed appreciable differences in the intensities of some peaks indicating that the two packings are indeed different. The molecules are planar with geometry similar to that found in form I (Table 5). Like in form I, the molecules are linked in infinite chains running parallel to the *a*-axis, *via* C-H…O hydrogen

bonds (Fig. 4, Table 6). These chains have a periodicity of eleven atoms, graph-set symbol C(11) according to Etter's graph-set theory.[65,66] In this polymorph there are also an intramolecular C-H···N hydrogen bond, forming six-membered rings with graph-set symbol S(6) and an intramolecular C-H...O hydrogen bond with graph-set symbol S(5) (Table 6).

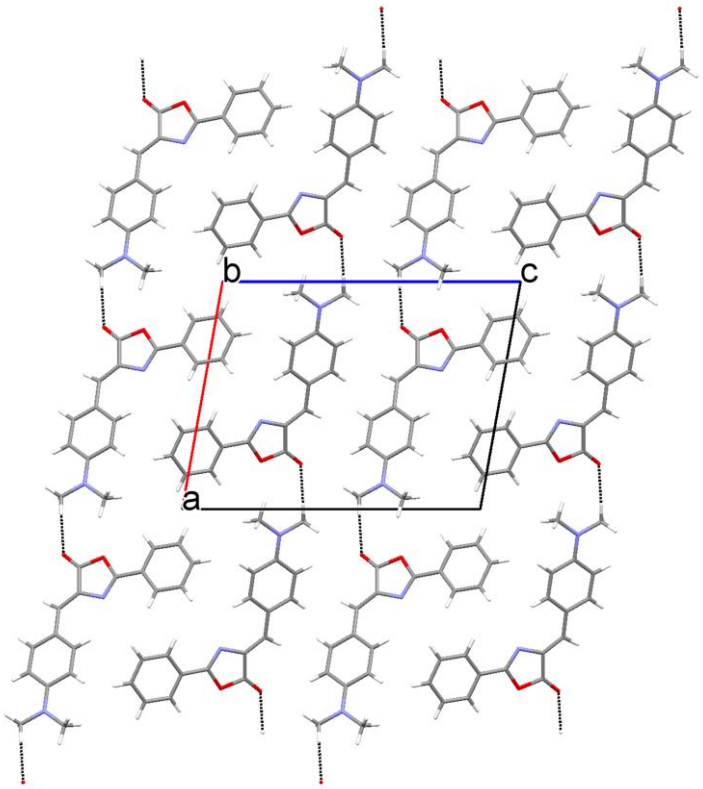


Figure 4 Packing diagram of polymorph II (**3a**) in a view along the *b* axis, with the H-bonds shown as dashed lines

Table 6 H-bond geometry (Å, º) of compound **3a**

	D-H	H...A	D...A	D-H...A
C2—H2C···O2^{i}	0.96	2.53	3.480(3)	172
C5—H5...N2 (intra)	0.93	2.47	3.111(3)	126
C18—H18...O1 (intra)	0.93	2.48	2.800(3)	100

(Symmetry code i: -1+x, -1+y, z)

The packing of the two polymorphs is remarkably similar viewed along the *b*-axis as can be seen in a whole-lattice overlay of the structures of the two forms (Fig. 5). However, if we look at the whole-lattice overlay along the *a*-axis (Fig. 6) we see clearly the different orientation of some molecules in forms I and II. In these whole-lattice overlays there are 2×2×2 unit cells of form II and 2×2×1 of form I.

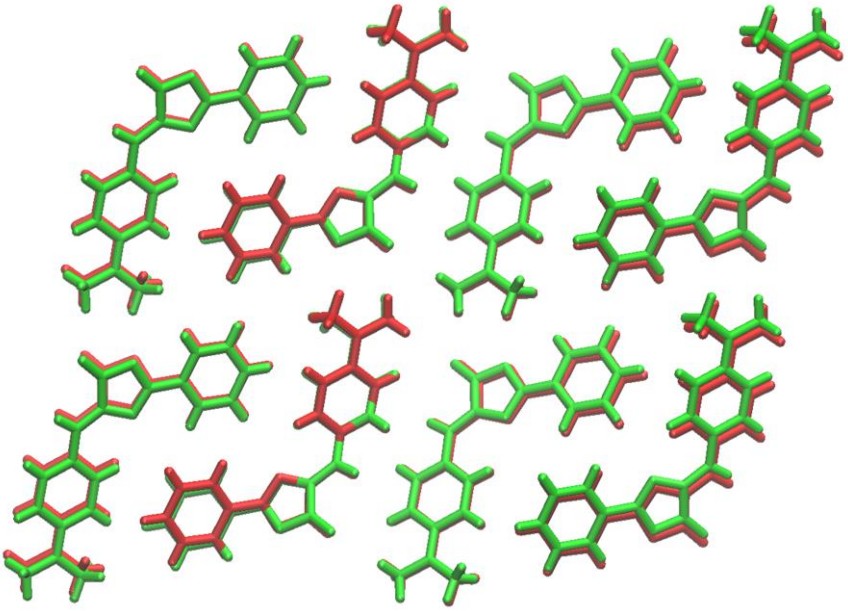


Figure 5 Whole-lattice overlays for structures of the form I (green) and form II (red) viewed along the *b*-axis

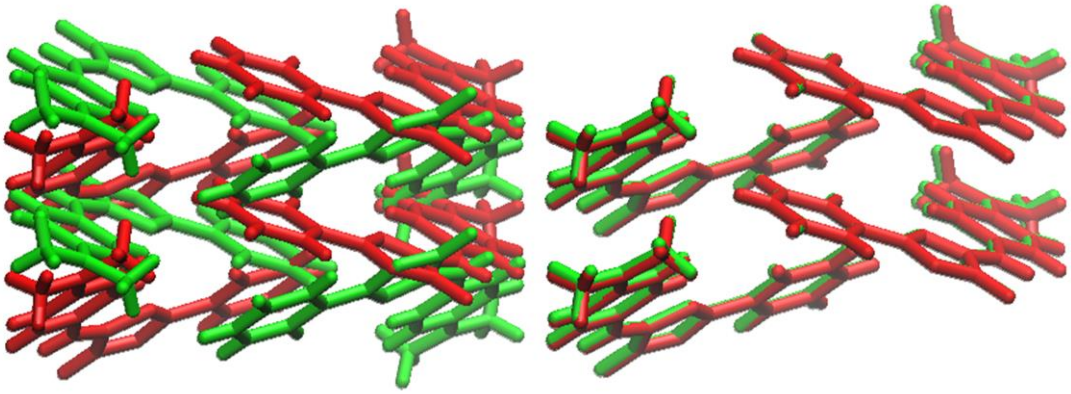
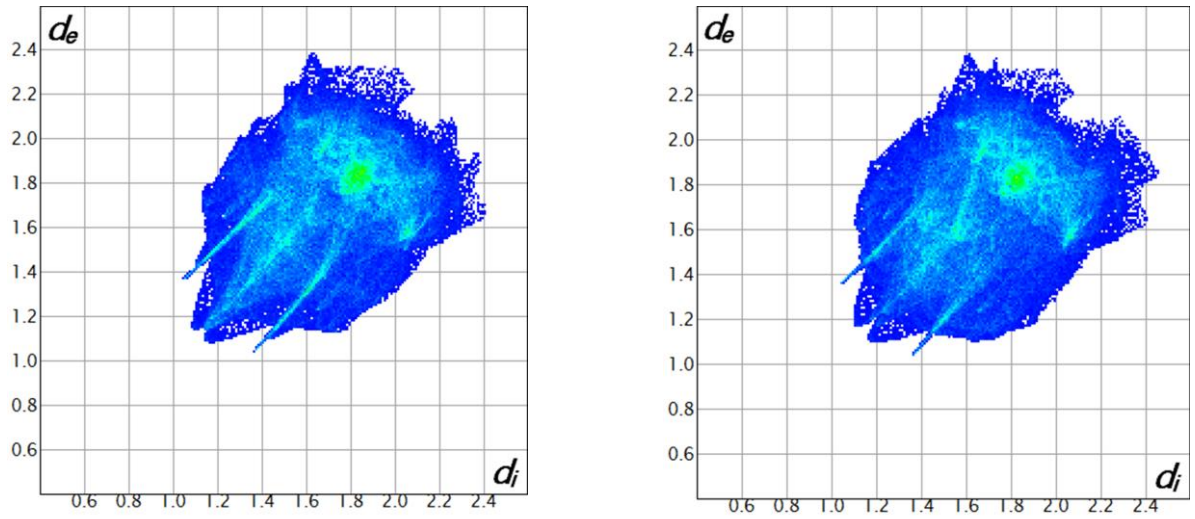


Figure 6 Whole-lattice overlays for structures of the form I (green) and form II (red) viewed along the *a*-axis

Fingerprint Plots

Comparing the same molecule in different crystal environments, Hirshfeld surfaces and fingerprint plots[67-70] have been shown to be a powerful tool for elucidating and comparing intermolecular interactions, especially in case of the study of polymorphism of molecular materials. The intermolecular interactions of this new polymorph and of the previously reported[63] were analysed using the two-dimensional fingerprint plots[69,70] derived from Hirshfeld surfaces,[67,68] using the software CrystalExplorer, version 3.1.[71] 2D-fingerprint plots were generated by using the *di* and *de* pairs measured on each individual spot of the calculated Hirshfeld surface. The 2D fingerprint plots of Form I and Form II are displayed in Fig. 7. The fingerprint plots have the same basic features, with both showing the presence of a pair of short sharp spikes, a characteristic of weak hydrogen bonding, in this case the C-H…O hydrogen bonds. The differences are more evident in the fingerprint plots of the O···H interactions (Fig. 8).



(a) **(b)**

Figure 7 Two-dimensional fingerprint plots for the polymorphs I (**a**) and II (**b**)

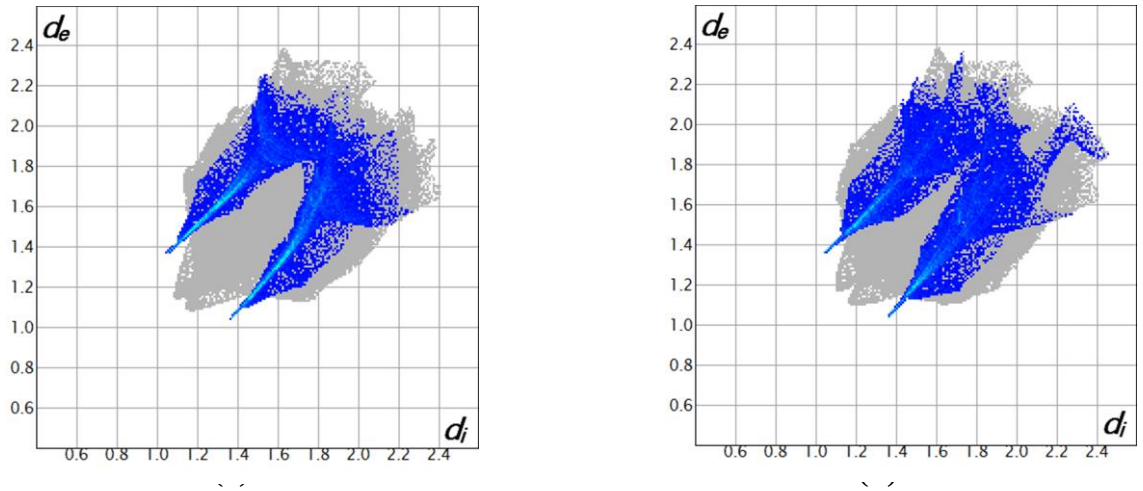


Figure 8 Two-dimensional fingerprint plots of the O…H interactions for the polymorphs I (**a**) and II (**b**)

XPac Analysis

The XPac program[72] allows the comparison of complete crystal structures and the quantification of their degree of similarity, based on the positions and geometric conformations of the molecules in the lattice. With this method it is possible to identify similar "supramolecular constructs" (sub-components of complete crystal structures) of 0-, 1- or 2-dimensionality in different crystal structures of specific molecules (polymorphs) or crystal structures of similar molecules (families) and of 3-dimensionality in isostructural assemblies.[73] In the XPac method, each crystal structure is represented by a cluster of molecules, with a central, core molecule and a shell of contacting molecules (usually 14). The two clusters are then compared by computing the mean differences δ_a(º) and δ_p(º) between all possible combinations of sets of angles and interplanar angles, respectively, between a chosen group of atoms in the core molecule and the corresponding atoms in one shell molecule.

The crystal structures of polymorphs I and II were compared with each other using the program XPac,[72] with geometric parameters generated from a set of 22 non-H atomic positions for each molecule. Each crystal structure was represented by a cluster consisting of

a central molecule and its 14 closest neighbours. Comparing the clusters of 14 neighbour molecules, 10 molecules were matched in the overlay, which corresponds to matching planes (similarity of 2D supramolecular constructs). In Fig. 9 it is presented a plot of δ_p against δ_a where we can see the high degree of similarity exhibited by the two structures. The vertical (blue) and horizontal (red) lines indicate the average values of δ_a and δ_p, 0.8º and 1.3º respectively. Each pair of values ($\delta_{a,i}$, $\delta_{p,i}$) provides information about how much the geometry of an assembly of two neighbour molecules deviates from the geometry of a second such assembly. The dissimilarity index x[74,75] is a measure of how far two structures deviate from perfect geometrical similarity and it is obtained from all M data points ($\delta_{a,i}$, $\delta_{p,i}$) that can be generated for the cluster under study.

$$x = 1/M \sum_{i=1}^{M} x_i = 1/M \sum_{i=1}^{M} \left(\delta_{a,i}^2 + \delta_{p,i}^2\right)^{1/2}$$

In the present study the dissimilarity index is 1.5. A value of zero corresponds to perfect geometric similarity. In conclusion, the XPac analysis demonstrates that crystal structures of forms I and II are very similar but not isostructural.

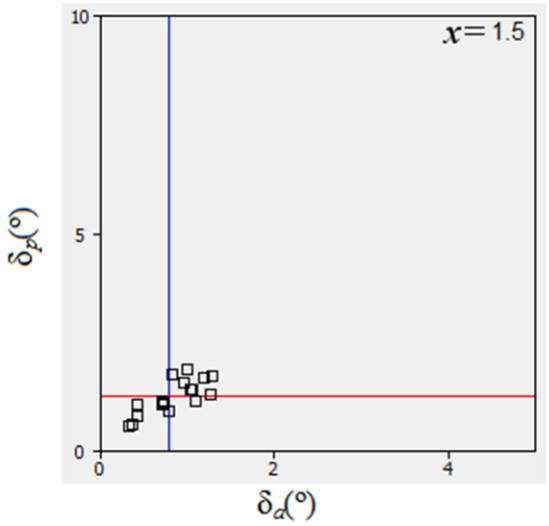


Figure 9 XPac plot of δ*p* against δ*a* (º). Upper right corner: dissimilarity index *x* (º)

Nonlinear optical properties

The crystal obtained in this study has some features that make it a potentially efficient nonlinear optical material: (i) absence of an inversion centre in the crystal structure; (ii) the molecule may have an appreciable hyperpolarizability since it has a strong electron donor (the dimethylamino group) connected by a conjugated π-bridge to the oxazolone group which acts as an electron acceptor in this case. To determine the NLO response of this new polymorph we measured the Second-Harmonic Generation (SHG) efficiency of the molecular crystal with the Kurtz-Perry method[76] using a polycrystalline sample. A good SHG efficiency of 1.4 times the urea standard was observed.

Experimental

Materials and general methods

All the reagents were purchased from Merck and Sigma-Aldrich (India) as 'synthesis grade' and used without further purification. Melting points of all synthesized compounds were determined on a Kofler apparatus and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded in the 400-4000 cm^{-1} wave-number range using a Perkin-Elmer (2000 FTIR) Spectrometer by the KBr pellet method. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-II 400 MHz instrument in $CDCl_3$ solvent. The chemical shifts (δ) are reported in ppm relative to the TMS as an internal standard and *J* values are reported in Hertz. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analysis (C, H and N) was conducted using a Thermo Scientific (FLASH 2000) CHN Elemental Analyser. Thin layer chromatography (TLC) glass plates coated with silica gel G254 (E-Merck) were used to check the purity of the reagent as well as the progress of the reaction.

Synthesis of ionic liquids

Triethylammonium sulfate [Et_3NH][HSO_4]. The [Et_3NH][HSO_4] ionic liquid was synthesized by the standard procedure as reported earlier in the literature .[57] ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.32 (t, 9H), 3.25 (m, 6H), 9.08 (s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.27 (CH_3), 59.35 (CH_2).

The various other ionic liquids i.e. [Pr_3NH][HSO_4], [Bu_3NH][HSO_4], [Et_3NH][H_2PO_4], [Bu_3NH][H_2PO_4], [Et_3NH][CH_3COO] and [Bu_3NH][CH_3COO] used for the comparative study with respect to [Et_3NH][HSO_4] were synthesized with the similar standard procedures as depicted in literature.[57]

n-Tributylammonium dihydrogen phosphate [Bu_3NH][H_2PO_4]. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.98 (t, 9H), 1.36 (m, 6H), 1.54 (m, 6H), 3.13 (m, 6H), 8.39 (s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 15.8 (C-4, CH_3), 20.5 (C-3, CH_2), 28.6 (C-2, CH_2), 57.9 (C-1, CH_2).

n-Tributylammonium acetate [Bu_3NH][CH_3COO]. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.94 (t, 9H), 1.31 (m, 6H), 1.49 (m, 6H), 3.23 (m, 6H), 8.29 (s, 1H, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 17.5 (C-4, CH_3), 22.3 (C-3, CH_2), 27.8 (C-2, CH_2), 58.2 (C-1, CH_2), 172.4 (C=O), 25.4 (CH_3).

General procedure for the synthesis of azlactones under solvent free conditions

The solution of hippuric acid **2** (2 mmol) and 20 mol% of the ionic liquids [Et_3NH][HSO_4] was allowed to stir at 80 ^{o}C for 5 min. After 5 min, aldehydes **1** (**a-q**) (2 mmol) was added to the reaction mixture and was further heated at 100 ^{o}C with constant stirring. After completion of the reaction as evident from thin layer chromatography (TLC), the reaction mixture was allowed to cool at room temperature and the reaction mixture solidified spontaneously. Then water was added to the reaction mixture and was further stirred for 5 min. The precipitate was

isolated by simple filtration, washed with appropriate solvents. The water was removed from filtrate under reduced pressure to recover the ionic liquid, which was then reused in subsequent cycles. The crude product obtained was recrystallized with chloroform-methanol to afford the pure product **3** (**a-q**).

Spectral Characterization

(*Z*)-4-(4-(dimethylamino)benzylidene)-2-phenyloxazol-5(4*H*)-one (3a)

Compound **3a** crystallized from $CHCl_3$-MeOH as red needle shaped crystal. Yield: 97%, m.p. 215 ^oC, reported 212-214 ^oC; Anal. calc. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58; found: C, 73.75; H, 5.69; N, 9.46. IR ν_{max}^{KBr} cm^{-1}: 1764 (C=O), 1642 (C=N), 1598 (C=C), 1192 (C-O)$_{lactone}$,. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.98 (s, 6H, 2 × CH_3), 7.18 (dd, 2H, H-3' and H-5'), 6.64 (dd, 2H, H-2' and H-6'), 7.36 (s, 1H, =C-H), 7.60-8.10 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.8 (C-1"),128.1 (C-2" and C-6"), 128.9 (C-3" and C-5"), 131.2 (C-4"), 163.8 (C-2), 141.6 (C-4), 175.3 (C-5), 129.8 (C-1'), 132.4 (C-2' and C-6'), 113.2 (C-3' and C-5'), 151.7 (C-4'), 134.8 (H-C=C), 44.1 (2 × CH_3). MS (ESI) m/z: 292.12 $[M+H]^{+\bullet}$.

(*Z*)-4-(4-fluorobenzylidene)-2-phenyloxazol-5(4*H*)-one (3b)

Compound **3b** crystallized from $CHCl_3$-MeOH as yellow crystalline solid. Yield: 95%, m.p. 181 ^oC, reported 183-185 ^oC;[29] Anal. calc. for $C_{16}H_{10}FNO_2$: C, 71.91; H, 3.77; N, 5.24; found: C, 71.88; H, 3.73; N, 5.27. IR ν_{max}^{KBr} cm^{-1}: 1778 (C=O), 1656 (C=N), 1594 (C=C), 1195 (C-O)$_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.32 (s, 1H, =C-H), 7.54 (dd, 2H, H-3' and H-5'), 7.98 (dd, 2H, H-2' and H-6'), 7.56-8.05 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 127.3 (C-1"), 128.1 (C-2" and C-6"), 129.6 (C-3" and C-5"), 132.8 (C-4"), 162.7 (C-2), 143.2 (C-4), 173.8 (C-5$_{(C=O)}$), 135.3 (H-C=C), 130.3 (C-1'), 133.8 (C-2' and C-6'), 116.8 (C-3' and C-5'), 163.4 (C-4'). MS (ESI) m/z: 267.07 $[M+H]^{+\bullet}$.

(*Z*)-4-(4-hydroxy-3-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (3c)

Compound **3c** crystallized from $CHCl_3$-MeOH as yellowish solid. Yield: 94%, m.p. 122-125 ^oC; Anal. calc. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74; found: C, 69.18; H, 4.41; N, 4.69. IR ν_{max}^{KBr} cm^{-1}: 3211 (O-H), 1767 (C=O), 1640 (C=N), 1597 (C=C), 1202 $(C\text{-}O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.43 (s, 1H, =C-H), 7.32 (d, 1H, H-6'), 7.21 (d, 1H, H-5'), 7.17 (s, 1H, H-2'), 5.28 (s, 1H, -OH), 3.52 (s, 3H, $-OCH_3$), 7.52-8.06 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 55.4 ($-OCH_3$) 127.5 (C-1"), 128.7 (C-2" and C-6"), 129.3 (C-3" and C-5"), 132.8 (C-4"), 162.4 (C-2), 141.8 (C-4), 171.6 $(C\text{-}5_{(C=O)})$, 135.4 (H-C=C), 132.4 (C-1'), 112.2 (C-2'), 152.5 (C-3'), 143.4 (C-4'), 115.8 (C-5'), 121.3 (C-6'). MS (ESI) m/z: 295.08 $[M+H]^{+\bullet}$.

(*Z*)-4-(4-nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (3d)

Compound **3d** crystallized from $CHCl_3$-MeOH as yellowish solid. Yield: 96%, m.p. 243 ^oC, reported 240-241 ^oC;[33] Anal. calc. for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52; found: C, 65.35; H, 3.39; N, 9.57. IR ν_{max}^{KBr} cm^{-1}: 1771 (C=O), 1648 (C=N), 1602 (C=C), 1528, 1342 (NO_2), 1208 $(C\text{-}O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.36 (s, 1H, =C-H), 7.96 (dd, 2H, H-2' and H-6'), 8.20 (dd, 2H, H-3' and H-5'), 7.62-8.05 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.9 (C-1"), 128.3 (C-2" and C-6"), 129.2 (C-3" and C-5"), 131.1 (C-4"), 161.7 (C-2), 142.6 (C-4), 173.2 $(C\text{-}5_{(C=O)})$, 134.8 (H-C=C), 138.2 (C-1'), 132.4 (C-2' and C-6'), 118.5 (C-3' and C-5'), 147.5 (C-4'). MS (ESI) m/z: 294.06 $[M+H]^{+\bullet}$.

(*Z*)-4-(3-nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (3e)

Compound **3e** crystallized from $CHCl_3$-MeOH as yellowish crystalline solid. Yield: 92%, m.p. 164 ^oC, reported 166-167 ^oC;[33] Anal. calc. for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52; found: C, 65.27; H, 3.48; N, 9.48. IR ν_{max}^{KBr} cm^{-1}: 1769 (C=O), 1652 (C=N), 1605 (C=C), 1526, 1344 (NO_2), 1205 $(C\text{-}O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.41 (s, 1H, =C-H), 8.54 (s, 1H, H-2'), 8.19 (dd, 1H, H-4'), 7.62 (t, 1H, H-5'), 7.84 (dd, 1H, H-6'), 7.50-7.95 (m, 5H,

ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 127.6 (C-1”), 128.8 (C-2” and C-6”), 129.1 (C-3” and C-5”), 131.8 (C-4”), 160.9 (C-2), 141.8 (C-4), 171.5 (C-$5_{(C=O)}$), 135.1 (H-C=C), 134.3 (C-1’), 121.7 (C-2’), 148.5 (C-3’), 125.4 (C-4’), 129.9 (C-5’), 132.8 (C-6’). MS (ESI) m/z: 294.06 $[M+H]^{+\bullet}$.

(*Z*)-4-((4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3f)

Compound **3f** crystallized from $CHCl_3$-MeOH as creamy crystalline solid. Yield: 93%, m.p. 205-207 ^{o}C; Anal. calc. for $C_{19}H_{11}NO_4$: C, 71.92; H, 3.49; N, 4.41; found: C, 71.96; H, 3.45; N, 4.43. IR ν_{max}^{KBr} cm^{-1}: 1745 $(C=O)_{lactone}$, 1654 $(C=O)_{\gamma\text{-}pyrone}$, 1646 (C=N), 1613 $(C=C)_{\gamma\text{-}pyrone}$, 1603 (C=C), 1201 $(C\text{-}O)_{lactone}$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.40 (s, 1H, =C-H), 7.95 (dd, 2H, H-5’ and H-8’), 7.50 (dd, 2H, H-6’ and H-7’), 7.28 (s, 1H, H-2’), 7.90-8.09 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.7 (C-1”), 129.1 (C-2” and C-6”), 129.9 (C-3” and C-5”), 131.9 (C-4”), 161.4 (C-2), 140.9 (C-4), 170.8 (C-$5_{(C=O)}$), 134.7 (H-C=C), 162.5 (C-2’), 115.4 (C-3’), 178.5 (C-$4'_{(C=O)}$), 122.6 (C-4’a), 124.2 (C-5’), 125.7 (C-6’), 134.2 (C-7’), 118.4 (C-8’), 154.5 (C-8’a). MS (ESI) m/z: 317.07 $[M+H]^{+\bullet}$.

(*Z*)-4-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3g)

Compound **3g** crystallized from $CHCl_3$-MeOH as orange colored solid. Yield: 94%, m.p. 210 ^{o}C; Anal. calc. for $C_{20}H_{13}NO_4$: C, 72.50; H, 3.95; N, 4.23; found: C, 72.86; H, 3.98; N, 4.21. IR ν_{max}^{KBr} cm^{-1}: 1748 $(C=O)_{lactone}$, 1651 $(C=O)_{\gamma\text{-}pyrone}$, 1639 (C=N), 1622 $(C=C)_{\gamma\text{-}pyrone}$, 1608 (C=C), 1206 $(C\text{-}O)_{lactone}$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.48 (s, 3H, $-CH_3$), 7.35 (s, 1H, =C-H), 6.96 (s, 1H, H-2’), 7.80 (s, 1H, H-5’), 7.42 (dd, 1H, H-7’), 7.32 (d, 1H, H-8’), 7.85-8.05 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 125.8 (C-1”), 127.9 (C-2” and C-6”), 128.6 (C-3” and C-5”), 131.3 (C-4”), 164.1 (C-2), 141.8 (C-4), 173.5 (C-$5_{(C=O)}$), 133.2 (H-C=C), 21.0 ($-CH_3$), 162.1 (C-2’), 117.8 (C-3’), 176.9 (C-$4'_{(C=O)}$), 122.0 (C-4’a), 123.4 (C-5’), 135.8 (C-6’), 138.3 (C-7’), 115.4 (C-8’), 154.0 (C-8’a). MS (ESI) m/z: 331.08 $[M+H]^{+\bullet}$.

(*Z*)-4-((6-bromo-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3h)

Compound **3h** crystallized from $CHCl_3$-MeOH as yellow powder. Yield: 93%, m.p. 197-199 ^oC; Anal. calc. for $C_{19}H_{10}BrNO_4$: C, 57.60; H, 2.54; N, 3.54; found: C, 57.63; H, 2.51; N, 3.57. IR ν_{max}^{KBr} cm^{-1}: 1752 $(C=O)_{lactone}$, 1658 $(C=O)_{\gamma\text{-}pyrone}$, 1643 (C=N), 1617 $(C=C)_{\gamma\text{-}pyrone}$, 1606 (C=C), 1204 $(C\text{-}O)_{lactone}$.^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.42 (s, 1H, =C-H), 7.23 (s, 1H, H-2'), 7.82 (s, 1H, H-5'), 7.50 (dd, 1H, H-7'), 7.32 (d, 1H, H-8'), 7.81-8.02 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 127.0 (C-1"), 128.9 (C-2" and C-6"), 129.8 (C-3" and C-5"), 131.7 (C-4"), 161.7 (C-2), 140.3 (C-4), 173.6 ($C\text{-}5_{(C=O)}$), 135.1 (H-C=C), 160.3 (C-2'), 119.2 (C-3'), 177.9 ($C\text{-}4'_{(C=O)}$), 122.9 (C-4'a), 123.8 (C-5'), 129.2 (C-6'), 134.3 (C-7'), 119.5 (C-8'), 153.6 (C-8'a). MS (ESI) m/z: 394.98 $[M+H]^{+\bullet}$.

(*Z*)-4-((6-fluoro-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3i)

Compound **3i** crystallized from $CHCl_3$-MeOH as yellow solid. Yield: 95%, m.p. 216 ^oC; Anal. calc. for $C_{19}H_{10}FNO_4$: C, 68.06; H, 3.01; N, 4.18; found: C, 68.03; H, 3.04; N, 4.20. IR ν_{max}^{KBr} cm^{-1}: 1756 $(C=O)_{lactone}$, 1665 $(C=O)_{\gamma\text{-}pyrone}$, 1647 (C=N), 1619 $(C=C)_{\gamma\text{-}pyrone}$, 1610 (C=C), 1209 $(C\text{-}O)_{lactone}$.^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.36 (s, 1H, =C-H), 7.21 (s, 1H, H-2'), 7.82 (s, 1H, H-5'), 7.54 (dd, 1H, H-7'), 7.29 (d, 1H, H-8'), 7.99-8.15 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.4 (C-1"), 128.2 (C-2" and C-6"), 129.4 (C-3" and C-5"), 131.9 (C-4"), 160.3 (C-2), 141.4 (C-4), 172.1 ($C\text{-}5_{(C=O)}$), 133.8 (H-C=C), 162.8 (C-2'), 118.3 (C-3'), 176.5 ($C\text{-}4'_{(C=O)}$), 125.2 (C-4'a), 121.8 (C-5'), 138.7 (C-6'), 124.1 (C-7'), 122.3 (C-8'), 150.9 (C-8'a). MS (ESI) m/z: 335.06 $[M+H]^{+\bullet}$.

(*Z*)-4-((6-chloro-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3j)

Compound **3j** crystallized from $CHCl_3$-MeOH as yellow crystalline solid. Yield: 96%, m.p. 204-206 ^oC; Anal. calc. for $C_{19}H_{10}ClNO_4$: C, 64.88; H, 2.87; N, 3.98; found: C, 64.91; H, 2.89; N, 3.95. IR ν_{max}^{KBr} cm^{-1}: 1753 $(C=O)_{lactone}$, 1661 $(C=O)_{\gamma\text{-}pyrone}$, 1645 (C=N), 1617 $(C=C)_{\gamma\text{-}pyrone}$, 1609 (C=C), 1207 $(C\text{-}O)_{lactone}$. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.38 (s, 1H, =C-

H), 7.28 (s, 1H, H-2'), 7.89 (s, 1H, H-5'), 7.63 (dd, 1H, H-7'), 7.25 (d, 1H, H-8'), 7.83-8.04 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.8 (C-1"), 128.7 (C-2" and C-6"), 129.2 (C-3" and C-5"), 132.0 (C-4"), 159.7 (C-2), 140.6 (C-4), 171.8 (C-$5_{C=O}$), 133.9 (H-C=C), 161.3 (C-2'), 117.9 (C-3'), 177.4 (C-$4'_{C=O}$), 122.9 (C-4'a), 123.5 (C-5'), 132.8 (C-6'), 135.8 (C-7'), 118.4 (C-8'), 152.8 (C-8'a). MS (ESI) m/z: 351.03 $[M+H]^{+\bullet}$.

(*Z*)-4-((1H-indol-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3k)

Compound **3k** crystallized from $CHCl_3$-MeOH as yellow crystalline solid. Yield: 94%, m.p. 210 °C, reported 207-208 °C;[33] Anal. calc. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; found: C, 74.96; H, 4.23; N, 9.70. IR ν_{max}^{KBr} cm^{-1}: 3442 (N-H), 1753 (C=O), 1641 (C=N)*lactone*, 1609 (C=C), 1215 (C-O)*lactone*. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.40 (s, 1H, =C-H), 7.53 (s,1H, H-2'), 8.35 (d, 1H, H-4'), 8.29 (m, 2H, H-5' and H-6'), 8.45 (dd, 1H, H-7'), 12.35 (s, 1H, -NH), 7.75-7.99 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.2 (C-1"), 128.1 (C-2" and C-6"), 128.9 (C-3" and C-5"), 131.2 (C-4"), 162.9 (C-2), 137.6 (C-4), 171.7 (C-$5_{C=O}$), 132.5 (H-C=C), 130.1 (C-2'), 116.4 (C-3'), 129.5 (C-3'a), 120.8 (C-4'), 121.8 (C-5'), 123.4 (C-6'), 112.1 (C-7'), 133.4 (C-7'a). MS (ESI) m/z: 288.09 $[M+H]^{+\bullet}$.

(*Z*)-4-((2-methyl-1H-indol-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3l)

Compound **3l** crystallized from $CHCl_3$-MeOH as yellowish solid. Yield: 95%, m.p. 198 °C; Anal. calc. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27; found: C, 75.46; H, 4.70; N, 9.25. IR ν_{max}^{KBr} cm^{-1}: 3435 (N-H), 1758 (C=O), 1640 (C=N)*lactone*, 1601 (C=C), 1206 (C-O)*lactone*. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.45 (s, 1H, =C-H), 2.18 (s, 3H, -CH_3), 8.28 (dd, 1H, H-4'), 8.17 (m, 2H, H-5' and H-6'), 8.39 (dd, 1H, H-7'), 12.17 (s, 1H, -NH), 7.82- 8.03 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.6 (C-1"), 128.9 (C-2" and C-6"), 129.8 (C-3" and C-5"), 131.8 (C-4"), 162.4 (C-2), 136.5 (C-4), 170.3 (C-$5_{C=O}$), 133.4 (H-C=C), 130.3 (C-2'), 117.6 (C-3'), 129.2 (C-3'a), 119.4 (C-4'), 120.9 (C-5'), 124.7 (C-6'), 113.8 (C-7'), 134.9 (C-7'a), 29.3 (-CH_3). MS (ESI) m/z: 302.11 $[M+H]^{+\bullet}$.

(*Z*)-4-((1H-pyrrol-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one (3m)

Compound **3m** crystallized from $CHCl_3$-MeOH as yellow crystalline solid. Yield: 97%, m.p. 182-184 ^oC; Anal. calc. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76; found: C, 70.60; H, 4.21; N, 11.72. IR ν_{max}^{KBr} cm^{-1}: 3439 (N-H), 1756 (C=O), 1638 $(C=N)_{lactone}$, 1611 (C=C), 1198 $(C-O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.41 (s, 1H, =C-H), 7.65 (s, 1H, H-2'), 7.35 (d, 1H, H-4'), 7.78 (d, 1H, H-5'), 11.96 (s, 1H, -NH), 7.71-7.93 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.8 (C-1"), 128.4 (C-2" and C-6"), 129.2 (C-3" and C-5"), 131.7 (C-4"), 161.3 (C-2), 136.4 (C-4), 170.1 ($C-5_{C=O}$), 132.7 (H-C=C), 127.3 (C-2'), 122.4 (C-3'), 115.9 (C-4'), 133.6 (C-5'). MS (ESI) m/z: 238.07 $[M+H]^{+\bullet}$.

(*Z*)-4-(benzofuran-3-ylmethylene)-2-phenyloxazol-5(4*H*)-one (3n)

Compound **3n** crystallized from $CHCl_3$-MeOH as light yellow powder. Yield: 92%, m.p. 215-216 ^oC; Anal. calc. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84; found: C, 74.71; H, 3.80; N, 4.88. IR ν_{max}^{KBr} cm^{-1}: 1762 (C=O), 1643 $(C=N)_{lactone}$, 1614 (C=C), 1208 $(C-O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.39 (s, 1H, =C-H), 8.09 (s, 1H, H-2'), 8.21 (d, 1H, H-4'), 7.72 (m, 2H, H-5' and H-6'), 8.05 (dd, 1H, H-7'), 7.85-7.99 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 126.2 (C-1"), 128.1 (C-2" and C-6"), 129.0 (C-3" and C-5"), 131.2 (C-4"), 159.9 (C-2), 136.3 (C-4), 171.8 ($C-5_{C=O}$), 133.5 (H-C=C), 139.7 (C-2'), 120.7 (C-3'), 124.7 (C-3'a), 121.3 (C-4'), 123.0 (C-5'), 125.9 (C-6'), 114.8 (C-7), 146.5 (C-7'a). MS (ESI) m/z: 289.07 $[M+H]^{+\bullet}$.

(*Z*)-4-(furan-3-ylmethylene)-2-phenyloxazol-5(4*H*)-one (3o)

Compound **3o** crystallized from $CHCl_3$-MeOH as pale yellow powder. Yield: 94%, m.p. 198 ^oC, reported 195-197 ^oC;[29] Anal. calc. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86; found: C, 70.31; H, 3.77; N, 5.85. IR ν_{max}^{KBr} cm^{-1}: 1765 (C=O), 1641 $(C=N)_{lactone}$, 1624 (C=C), 1203 $(C-O)_{lactone}$. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.35 (s, 1H, =C-H), 8.11 (s, 1H, H-2'), 7.55 (d, 1H, H-4'), 7.92 (d, 1H, H-5'), 7.73-7.97 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):

127.3 (C-1”), 128.8 (C-2” and C-6”), 129.9 (C-3” and C-5”), 131.4 (C-4”), 160.7 (C-2), 137.4 (C-4), 172.5 (C-$5_{C=O}$), 132.7 (H-C=C), 134.3 (C-2’), 122.8 (C-3’), 110.8 (C-4’), 141.2 (C-5’). MS (ESI) m/z: 239.06 $[M+H]^{+\bullet}$.

(*Z*)-4-(benzo[b]thiophen-3-ylmethylene)-2-phenyloxazol-5(4*H*)-one (3p)

Compound **3p** crystallized from $CHCl_3$-MeOH as yellow solid. Yield: 93%, m.p. 195-197 ^oC; Anal. calc. for $C_{18}H_{11}NO_2S$: C, 70.80; H, 3.63; N, 4.59; found: C, 70.83; H, 3.67; N, 4.62. IR ν_{max}^{KBr} cm^{-1}: 1758 (C=O), 1643 (C=N)*lactone*, 1619 (C=C), 1211 (C-O)*lactone*. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.43 (s, 1H, =C-H), 8.12 (s, 1H, H-2’), 7.93 (d, 1H, H-4’), 7.57 (m, 2H, H-5’ and H-6’), 7.70 (dd, 1H, H-7’), 7.79-7.94 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 127.4 (C-1”), 128.8 (C-2” and C-6”), 129.5 (C-3” and C-5”), 131.1 (C-4”), 161.7 (C-2), 137.5 (C-4), 170.8 (C-$5_{C=O}$), 133.9 (H-C=C), 130.5 (C-2’), 132.2 (C-3’), 133.5 (C-3’a), 122.3 (C-4’), 124.7 (C-5’), 125.8 (C-6’), 118.6 (C-7’), 142.6 (C-7’a). MS (ESI) m/z: 305.05 $[M+H]^{+\bullet}$.

(*Z*)-4-(thiophen-3-ylmethylene)-2-phenyloxazol-5(4*H*)-one (3q)

Compound **3q** crystallized from $CHCl_3$-MeOH as bright yellow solid. Yield: 95%, m.p. 172 ^oC; Anal. calc. for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49; found: C, 65.85; H, 3.58; N, 5.52. IR ν_{max}^{KBr} cm^{-1}: 1763 (C=O), 1639 (C=N)*lactone*, 1612 (C=C), 1207 (C-O)*lactone*. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.35 (s, 1H, =C-H), 7.97 (s, 1H, H-2’), 7.45 (d, 1H, H-4’), 7.80 (d, 1H, H-5’), 7.84-7.98 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 127.1 (C-1”), 128.5 (C-2” and C-6”), 129.2 (C-3” and C-5”), 131.3 (C-4”), 161.2 (C-2), 136.2 (C-4), 171.3 (C-$5_{C=O}$), 132.8 (H-C=C), 131.9 (C-2’), 128.2 (C-3’), 117.4 (C-4’), 137.2 (C-5’). MS (ESI) m/z: 255.04 $[M+H]^{+\bullet}$.

Computational Methods

Crystal structure determination

A crystal of the model compound **3a** suitable for an X-ray diffraction study, with needle habit and having approximate dimensions of 0.60 mm × 0.13 mm × 0.11 mm, was glued on a glass fibre and mounted on a Bruker Apex II diffractometer. The diffraction data was collected at room temperature 293(2) K using graphite monochromated Mo Kα (λ = 0.71073 Å). Data reduction was performed with APEX II.[77] Lorentz and polarization corrections were applied. Absorption correction was applied using SADABS.[78] The crystallographic structure was solved using direct methods (SHELXS-97).[79] The structure refinement was carried out with SHELXL-97 software.[79] The refinement was made by full-matrix least-squares on F2, with anisotropic displacement parameters for all non-hydrogen atoms. All the hydrogen atoms were located in a difference Fourier synthesis, placed at calculated positions and then, included in the structure factor calculation in a riding model using SHELXL-97 defaults. MERCURY 3.3[80] was used for figure plotting. PLATON[64] was used for hydrogen bond interactions. Additional information to the structure determination is given in Table 7. Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with reference number CCDC 1039655.

Table 7 Crystallographic data and structure refinement of compound **3a**

Empirical formula	$C_{18}H_{16}N_2O_2$
Formula weight	292.33
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	12.0978(3)
b (Å)	3.97900(10)
c (Å)	15.5788(4)
α (^{o})	90
β (^{o})	100.0550(10)
λ (^{o})	90
Volume (Å^3)	738.40(3)
Z	2
Calculated density (g/cm^3)	1.315
Absorption coefficient (mm^{-1})	0.097
F(000)	308
Crystal size (mm)	0.60 × 0.13 × 0.11
θ range for data collection (^{o})	3.41-26.05
Index ranges	$-14 < h < 14$, $-4 < k < 4$, $-19 < l < 18$
Reflections collected/unique	13647/2873 [*R(int)* = 0.0208]
Completeness to $\theta = 25.00^o$	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2873/1/201
Goodness-of-fit on F^2	1.040
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0352 *wR2* = 0.0877
R indices (all data)	*R1* = 0.0422 *wR2* = 0.0924
Largest diff. peak and hole (e Å^{-3})	0.135 and -0.180

DFT calculations

The geometry optimization was performed using the PC GAMESS/Firefly QC package [81], which is partially based on the GAMESS (US) source code,[82] starting from the experimental X-ray geometry (*Z*-isomer). The calculation was performed within density functional theory (DFT) using B3LYP (Becke three–parameter Lee–Yang–Parr) for exchange and correlation, which combines the hybrid exchange functional of Becke[83,84] with the correlation functional of Lee, Yang and Parr.[85] The calculation was performed with an extended 6-311G(d,p) basis set. Tight conditions for convergence of both the self-consistent field cycles and the maximum density and energy gradient variations were imposed (10-5 atomic units). At the end of this geometry optimization we conducted a Hessian calculation to guarantee that the final structure corresponds to a true minimum, using the same level of theory as in the geometry optimization.

The geometry of the *E*-isomer was also optimized with the same level of theory. The starting geometry of the *E*-isomer used for the optimization was obtained from the optimized geometry of the *Z*-isomer, performing the necessary rotation of torsion angle using the UCSF Chimera software package version 1.8.[86] For the optimized geometries of the *Z* and *E*-isomers we performed single-point energy calculations with the conditions mentioned above (DFT: B3LYP functional and 6–311G(d,p) basis set).

Kurtz-Perry Powder Method

The Second-Harmonic Generation (SHG) efficiency of the new polymorph of the model compound **3a** was measured using the Kurtz and Perry powder method.[76] The measurements were performed at a wavelength of 1064 nm produced by a Nd:YAG laser operating at 10 Hz and producing 10 ns pulses with a pulse energy of 11 mJ. The sample preparation procedure was as follows: the material was mulled to a fine powder and compacted in a mount and then

installed in the sample holder. Sample grain sizes were not standardized. Signals between individual measurements were seen to vary in some cases by as much as ±10%. For a proper comparison with the urea reference material the measurements were averaged over several laser thermal cycles.

Conclusions

The present protocol reports convenient and eco-friendly approach for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones in excellent yields in ionic liquid $[Et_3NH][HSO_4]$. This solvent-free, green synthetic procedure eliminates the use of toxic acetic anhydride and promotes selectivity towards *Z*-azlactones/oxazolone. The noteworthy feature of this synthetic strategy is that, the ionic liquid possesses both catalytic as well as medium engineering potential in this protocol. The ionic liquid $[Et_3NH][HSO_4]$ employed in the present study exhibits stability towards moisture and air and is easy to prepare from cheap acid and amine. The scheme not only offers substantial yield of products and shorter reaction time but also affords mild reaction conditions, high purity, cleaner reaction profile, operational simplicity, enhanced reaction rates and easy workup procedure. The present protocol possesses wide substrate tolerance. We believe that this synthetic approach provides a better scope for the synthesis of *Z*-azlactones/oxazolone and will be a more practical alternative to the other existing methods.

Acknowledgements

F. Ahmad thanks the Chairman, Department of Chemistry, AMU, Aligarh, for providing the necessary research facilities. Sophisticated Analytical Instrumentation Facility (SAIF), Panjab University, Chandigarh, is credited for spectral analysis. CEMDRX Physics

Department, University of Coimbra, Portugal is acknowledged for X-ray analysis. UGC is also gratefully acknowledged for research fellowship to F. Ahmad and S. Azaz.

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