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PII: S0040-4020(16)31272-8

DOI: 10.1016/j.tet.2016.12.004

Reference: TET 28296

To appear in: *Tetrahedron*

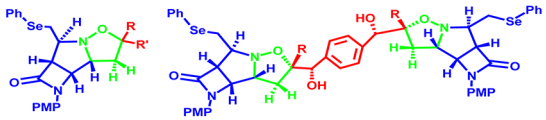
Received Date: 11 August 2016

Revised Date: 20 November 2016

Accepted Date: 6 December 2016

Please cite this article as: Periyasami G, Arumugam N, Aldalbahi A, Inexpensive ionic liquid mediated green synthetic approach of multi-functionalized regioselective β-lactam fused isoxazolidine heterocyclic hybrids, *Tetrahedron* (2017), doi: 10.1016/j.tet.2016.12.004.

Quaternary ammonium salt based room temperature ionic liquid, ACI/EG utilized for the synthesis of isoxazolidine heterocyclic hybrids by the addition of beta lactam fused nitrone with number of mono/bis O-allylic dipolarophiles. Exclusive regioselectivity with excellent chemical yield was achieved.



R=COOMe, COOEt, CN; R′ = Aromatic diketone derivatives

Inexpensive ionic liquid mediated green synthetic approach of multi-functionalized regioselective β-lactam fused isoxazolidine heterocyclic hybrids

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Abstract: A novel efficient eco-friendly on "ionic liquid" method has been developed for the synthesis of multi-functionalized isoxazolidines through a nitrone 1,3-dipolar cycloaddition reaction. The low cost and eco-benign room temperature ionic liquid, acetylcholine iodide-ethylene glycol (ACI/EG) accelerates the formation of the desired regioselective mono-/di isoxazolidine analogues and reduced the reaction time with high level of chemical yield. Furthermore, the recyclability of ACI/EG has also been investigated.

Key words: Nitrone Cycloaddition, Isoxazolidines, β-Lactam, Regioselectivity, Ionic liquid.

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1. Introduction

Beyond their well-known biological properties, oxazolidine derivatives and various *β*-lactam antibiotics have also been used as building blocks in the stereo controlled synthesis of complex organic compounds.[1] Isoxazolidine functional group play key roles in several transformations,[2] and their analogues are interesting intermediates for the synthesis of β-amino alcohol and alkaloids. In particular, one of the highly biological active *Gelsemium* alkaloids and their building blocks can be synthesized from isoxazolidine analogues by ring contraction.[2d] Modified spiro isoxazolidines have also been proved to efficiently inhibit *in vitro* and *in vivo* viral infections caused by sexual transmission.[3] In addition, functionalized isoxazolidine derivatives are known to possess antifungal, anti-inflammatory, antiviral, and herbicidal properties.[4] Azetidine-2-

one is an another important heterocyclic scaffold as it is prevalent in many antibiotics such as penicillins, cephalosporins, carbapenems, nocardicins and monobactams.[5]

Based on the precedents outlined above, we reasoned the combination of the isoxazolidine and azetidine-2-one motifs in a single molecule would be of interest in the context of antimicrobial drug discovery.[6] Accordingly, research in exploring strategies for the preparation of functionalized novel isoxazolidine analogues were fascinating for many decades and it can be effectively synthesized from 1,3-dipolar cycloaddition reaction between nitrones and electron deficient dipolarophiles. Certainly, 1,3-dipolar cycloaddition reaction is one of the best known methods to afford, particularly 5-membered heterocyclic derivatives due to its direct, regio-specific, and stereo-controlled approach.[7] Particularly, nitrone cycloaddition is a quite useful method for the construction of nitrogen-containing carbon frameworks *i.e.*, carbon-carbon bonds (C=C) and carbon-oxygen bonds (C=O) in a one- pot reaction.

Considering the growing environmental impacts of organic volatile solvents, organic reactions conceded on 'green solvents' like ionic liquids (ILs) have become one of the most absorbing area in environmentally benign chemistry. Despite their green credentials,[8] many of the IL reactions require high temperature, prolonged reaction time and complicated purification processes. The choice of room temperature ionic liquids (RTILs) in organic synthesis overcome those limitations besides their easy obtainability. Particularly, imidazolium ionic liquids possess excellent ionic conducting nature and low volatilities, and are thus encouraging to be utilized as an alternative to the commonly used organic solvents for eco-friendly reactions.[9] In 2008, considering their cost effect and drastic conditions, Jhong *et al.*,[10] made attempt to prepare quaternary ammonium salts based RTILs. Recently, S-Y Lu *et al.*[11] synthesized low price quaternary ammonium salts based RTILs called acetylcholine iodide-ethylene glycol (ACI/EG) and utilized as low volatile electrolyte for dye sensitized solar cells. ACI/EG RTILs can be easily prepared by simply mixing and heating quaternary ammonium salt acetylcholine iodide (ACI) with hydrogen bond donor ethylene glycol (EG). RTILs gains importance due to their simple preparation and unexplored solvent medium in nitrone cycloaddition reactions.

2. Results and Discussion

We chose novel β-lactam fused bicyclic nitrone and hydroxy allylic ketone derivatives prepared from vinyl β-lactam aldehyde and vinyl ester / nitrile, respectively. The hydroxy allylic Baylis-Hillman (BH) adduct would be of great interest as alkenes have proven to be useful precursors for the synthesis of multifunctional heterocycles and biologically active molecules.[12] Besides that the hydroxy allylic BH adduct was efficient dipolarophile due to the presence of electron withdrawing group. The synthetic strategy used for construction of highly regioselective isoxazolidines is shown in Figure 1.

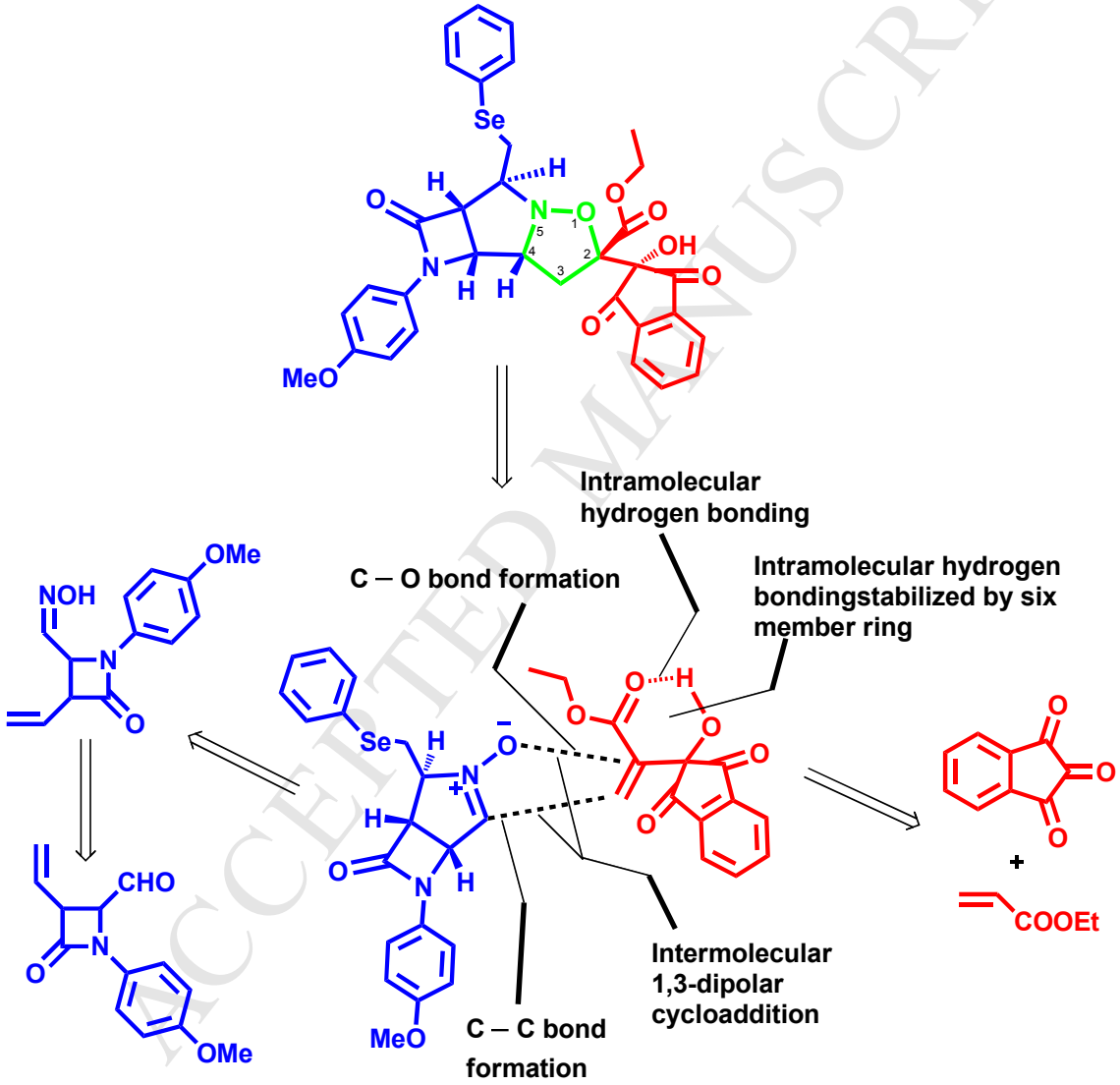
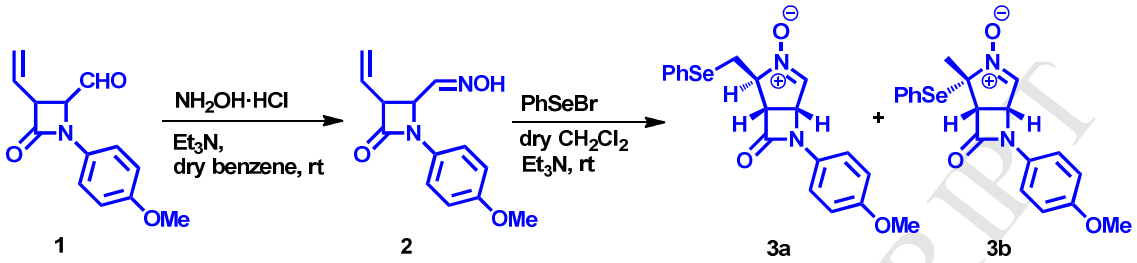


Figure 1. Synthetic strategy of β-lactam fused polycyclic isoxazolidine moieties.

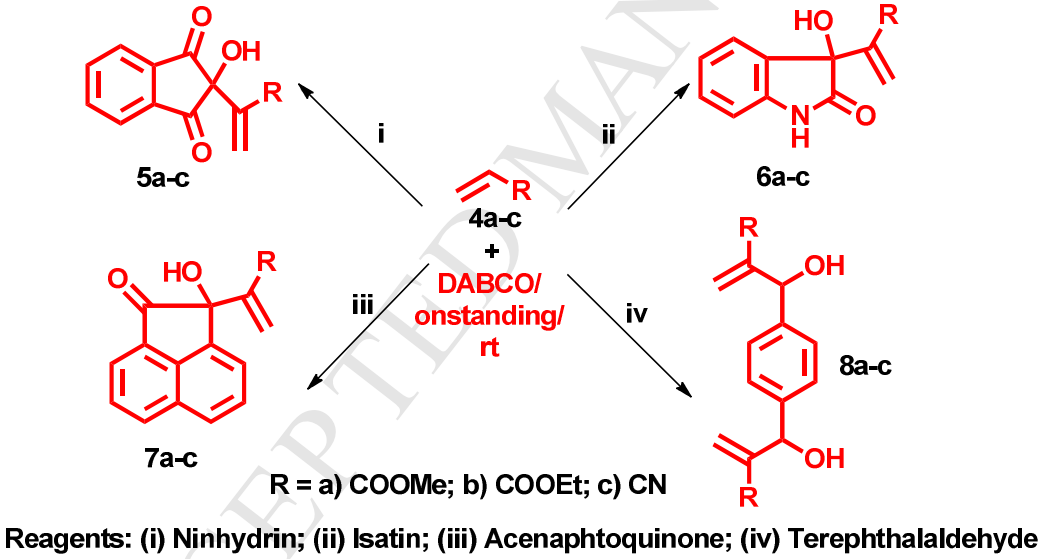
β-Lactam bicyclic nitrones were prepared,[13, 6a] as regioisomeric mixture in good yield, by the reaction of vinyl *β*-lactam aldehyde **1** with hydroxylamine hydrochloride

in the presence of Et_3N. Initially β–lactam oxime **2** was obtained, which was then treated with phenylselenyl bromide in dry CH_2Cl_2 at room temperature followed by the addition of Et_3N to furnish the bicyclic nitrones **3a** and **3b** (67:33), which were easily separated by flash column chromatography (Scheme 1).



Scheme 1. Synthesis of β-lactam fused phenylselenylbicyclic nitrone **3a** and **3b**

The various required substituted hydroxy allylic BH adducts were prepared (Scheme 2) by the reaction of corresponding di/tri ketone with acrylates in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as base.[14]



Scheme 2. Synthesis of hydroxy allylic BH adducts

The synthesized dipolarophiles (**5a-c** to **8a-c**) are highly stable, possibly due to the presence of intramolecular hydrogen bonding between electron withdrawing groups and oxygen atom in OH group. An IR absorption band confirms our observation and the OH group exhibit a lower frequency broad band at ~3250 cm^{-1} due to intramolecular hydrogen bonding between allylic OH and ester carbonyl oxygen / nitrile nitrogen group.[15a] In the case of nitrile substitution (eg. **5c**), the CN absorption band is at ~2123 cm^{-1}, which is in good agreement with Buckingham formula describing the frequency

shift.[15b-d] Also the C=O stretching absorption peak appeared at the range of 1690 cm^{-1} to 1706 cm^{-1}. From the above observations, it is clear that the availability of favored alkene position for cycloaddition is stabilized by weak O─H···O=C / O─H···N≡C intramolecular hydrogen bonds and the O-allylic alkene bond formation is stabilized by stable six member ring (Figure 2).

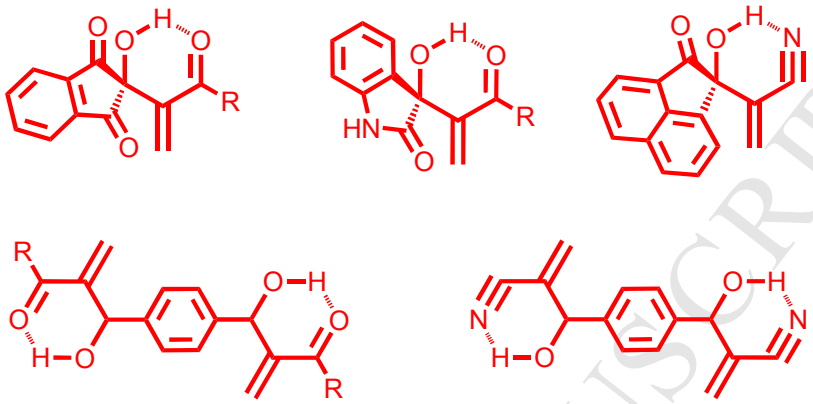


Figure 2. Intramolecular hydrogen bonding between electronegative atoms of BH adducts

After extensive experimentation in various solvents (organic solvents and ionic liquids) and reaction conditions like various temperature with various time interval, we established that the cycloadducts were obtained in high yields by using ACI/EG RTIL as a suitable medium at room temperature condition. This optimized reaction conditions were investigated (Table 1) by the reaction of an equimolar quantity of hydroxy allylic BH adduct **5a** derived from ninhydrin and methylacrylate **4a**, with isolated 1,3-dipolar, *β*-lactam fused phenylselenylbicyclic nitrone **3a** furnished indanedione substituted β-lactam fused polycyclic novel isoxazolidines **9a** in ACI/EG RTIL medium at room temperature. The cycloadducts **9a** was obtained around ~15% to 20% yield in organic solvents. The same reactant undergoing cycloaddition in ILs gives better chemical yield from 43% to 55% even though it requires temperature for activation. But, the ACI/EG RTIL medium afforded excellent yield 92% with high selectivity and also in shorter reaction time at room temperature. The used ACI/EG was recovered by vacuum distillation and dried under vacuum at 40 °C overnight and then recycled. The utility of recovered RTIL was presented in Table 2.

Table 1. Solvent condition and reaction time optimization of cycloaddition

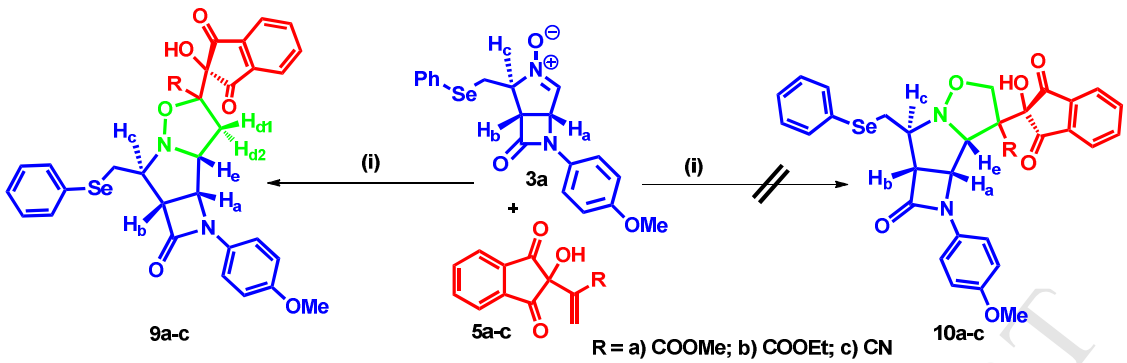
Entry	Solvent system	Time (h)	Yield (%)
1	Ethanol	48	20
2	Methanol	48	20
3	Acetonitrile	48	trace
4	Dry MeCN	24	20
5	Dry dioxane	48	-
6	Dioxane/MeCN (1:1)	24	15
7	[Bmim][Cl]	6	43
8	[Bmim][Br]	6	52
9	[Bmim][Tfa]	6	48
10	[Bmim][PF_6]	8	46
11	[Bmim][BF_4]/CuI (10 mol%)	8	44
12	[Bmim][BF_4]/Cu(OTf) (10 mol%)	6	55
13	**ACE/EG, rt**	1	92
14	ACE/EG, 60 °C	2	90

General conditions: Optimized reaction conditions are in bold (entry 13, 14)
Ionic liquids were subjected to high vacuum before use (entry 7-14)

Table 2. Reusability in various cycles of recovered ACE/EG in the synthesis of **5a** at room temperature

Medium	Yield percentage of isoxazolidine **5a** in experiments				
	First	Second	Third	Fourth	Fifth
Recovered ACE/EG	90	90	87	87	85

The synthesis of indanedione substituted β-lactam fused polycyclic novel isoxazolidines (**9a-c)** was achieved by the addition of an equimolar quantity of hydroxy allylic BH adduct (**5a-c)** derived from ninhydrin, with isolated 1,3-dipolar, *β*-lactam fused phenylselenylbicyclic nitrone **3a**, in ACI/EG RTIL medium at room temperature (Scheme 3).

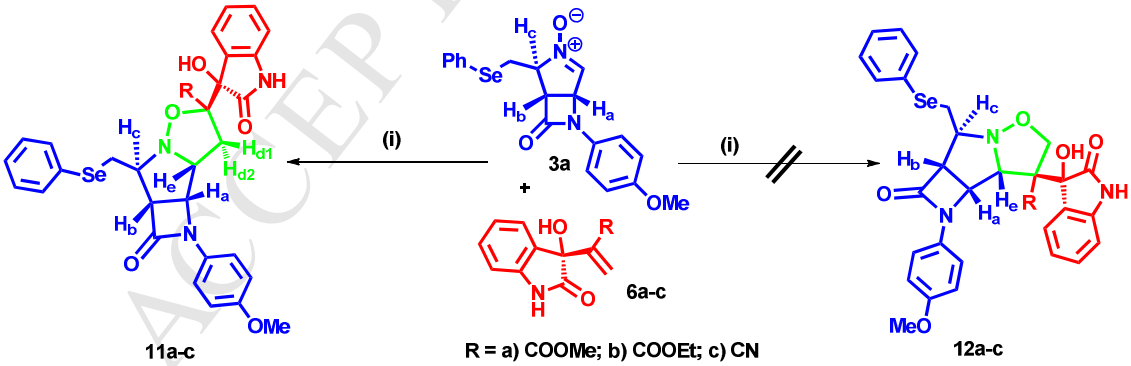


Reagents and conditions: (i) ACI/EG RTIL; Stirring at room temperature

Scheme 3. Synthesis of β-lactam fused polycyclic isoxazolidines **9a-c**

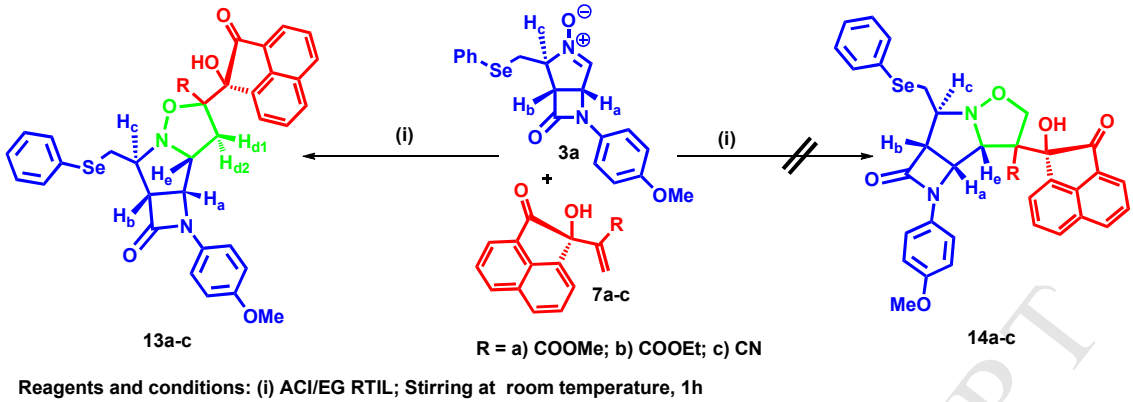
The systematic structure analysis for the synthesized cycloadducts to arrive at the proposed regiochemistry was carried out using one and two-dimensional NMR spectroscopic techniques. For instance, the IR spectrum of cycloadduct **9b** showed three characteristic peaks at 1755 cm^{-1}, 1740 cm^{-1} and 1703 cm^{-1} due to *β*-lactam and ninhydrin carbonyl carbons. The regiochemistry of the cycloadduct **9b** was initially determined by its ^{1}H NMR spectrum, which showed two multiplets in the range δ = 2.43–2.50 ppm and δ = 2.74–2.80 ppm corresponding to isoxazolidine ring methylene. The presence of two multiplets instead of two doublets for isoxazolidine ring diastereotopic methylene protons strongly ruled out the formation of other regioisomer **10b**. That the H_d proton shows multiplet between δ = 2.43-2.80 ppm supports formation of regioisomer **9b**. The ^{13}C NMR spectrum of **9b** exhibited a peak at δ = 164.5 ppm and δ = 168.9 ppm due to *β*-lactam and ester carbonyl carbons, respectively. The peaks at δ = 194.4 ppm and δ = 197.6 ppm corresponded to two carbonyl carbons of the ninhydrin moiety. The quaternary carbon showed a peak at δ = 85.8 ppm. The off-resonance decoupled ^{13}C NMR spectrum of **9b** showed a triplet at δ = 29.8, δ = 34.5 and δ = 63.4 due to three methylene carbons in the cycloadduct which is also confirmed by DEPT-135 NMR spectrum. ^{1}H–^{1}H COSY studies indeed showed that cross-peaks were observed among H_a–H_e, H_a–H_b; H_b–H_c, H_b–H_a; H_e–H_{d1} and H_e–H_{d2} resonances, whereas the ^{1}H–^{13}C COSY spectra showed connectivity between the methylene carbons with corresponding methylene protons; thus, δ_C = 60.8 (*J* = 3.67–3.72); δ_C = 34.5 with H_d protons and δ_C = 29.9. Furthermore, the presence of the molecular ion peak at *m*/*z* 661.56 (M+) in the mass spectrum of **9b** supported the formation of the cycloadduct and the compound gave satisfactory elemental analysis.

With the background of theoretical studies, the regioselectivity and endo/exo ratio of nitrone type dipolar cycloaddition reaction depends on the nature of the dipolarophile, related to the size of reactants and several environmental factors of the reaction including solvent systems.[16] As we used RTILs as highly polar solvent medium and the highly rigid dipolar and dipolarophile support the formation of cycloadduct through less hindered facial selectivity. The assignments of all the hydrogens and carbons of cycloadduct **9b** will be essential for stereochemistry and regiochemistry determination, particularly the multiplicity between H_c and H_d protons confirms the regiochemistry of the cycloadduct. Also, the absence of interaction between OH proton with H_d protons for methylene protons of isoxazolidine ring shows that the intramolecular hydrogen bond between OH and COOEt is undisturbed during the formation of cycloadducts. In addition, the intramolecular hydrogen bonding in BH dipolarophile causes the lowering of $LUMO_{alkene}$ energy level and reduction of the $HOMO_{alkene}/LUMO_{nitrone}$ energy gap.[17] Such an interaction also influenced the regioselectivity of adducts during the formation for transition state in addition reaction. As it can be seen from the above discussion, the formation of regioisomer **9b** is highly favorable and the unfavorable environment for the formation of regioisomer **10b**. Similar results were observed when the reaction was carried out with isatin dipolarophiles (**6a-c**) giving cycloadducts (**11a-c**) in Scheme 4 and acenaphthoquinone dipolarophiles (**7a-c**) giving cycloadducts (**13a-c**) in Scheme 5 respectively. The NMR spectra details were discussed in the experimental section and spectra were presented in supporting information.†



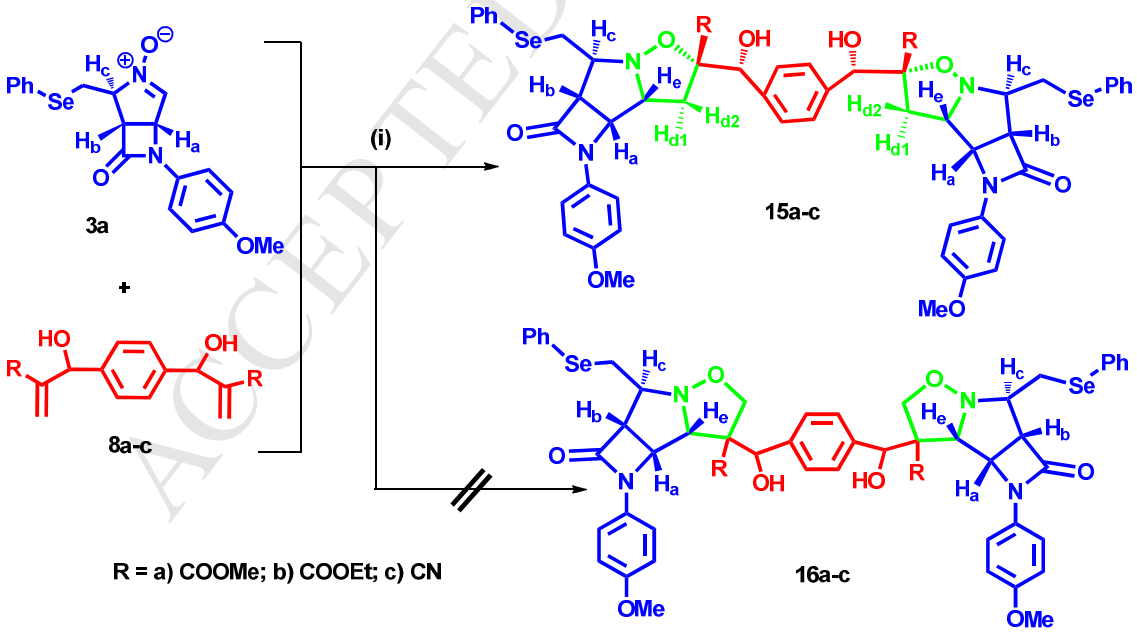
Reagents and conditions: (i) ACl/EG RTIL; Stirring at room temperature

Scheme 4. Synthesis of β-lactam fused polycyclic isoxazolidines **11a-c**



Scheme 5. Synthesis of β-lactam fused polycyclic isoxazolidines **13a-c**

Motivated by the aforementioned results, we sought to extend the scope of the cycloaddition methodology using methyl 1,4-bis-(3-hydroxy-2-methylenebutanoatonyl) benzenes (**8a-c)**, as an bis-dipolarophile with bicyclic nitrone **3a**. Synthesis of aryl-bridged bis-isoxazolidines (**15a-c**) was accomplished by reacting 2.2 equivalent of bicyclic nitrone **3a** with one equivalent of bis-hydroxy allylic BH adducts (**8a-c)** in ACI/EG RTIL medium at room temperature. As per our expectation, on extension of this methodology to these reactions, the regiochemistry of the product remained unchanged, as observed in the previous schemes (Scheme 6).



Scheme 6. Synthesis of β-lactam fused polycyclic isoxazolidines **15a-c**

The structure of regioisomers was elucidated using standard spectroscopic studies. Considering an example of nitrile substituted adduct **15c**, in the ^{1}H NMR spectrum, it showed a singlet at δ = 5.10 ppm due to the benzylic proton. As observed in the earlier case, isoxazolidine ring methylene protons resonate as two multiplets in the range δ = 2.51-2.57 ppm and δ = 2.87-2.95 ppm which confirm the regiochemistry of the cycloadduct. The presence of these two multiplets and the absence of two doublets for isoxazolidine diastereotopic methylene protons strongly ruled out the formation of other regioisomer **16c**. The ^{13}C NMR spectrum of **15c** exhibited a peak at δ = 163.8 ppm due to *β*-lactam carbonyl carbon. The peak corresponding to CN attached quaternary carbon appeared at δ = 80.9 ppm and, DEPT-135 studies confirmed that two methylene carbons are present in the cycloadduct at δ = 30.5 and δ = 35.8 ppm. The mass spectrum of compound **15c** exhibited molecular ion peak at MALDI-TOF *m/z* 1042.88 (M^{+}), which confirmed the formation of cycloadduct and the compound gave satisfactory elemental analysis. Similar results were observed for the cycloadducts **15a** and **15b**. NOE irradiation of OH proton in **15c** at δ = 2.17 did not cause any enhancement of the signal for H_{d1} and H_{d2} protons of isoxazolidinyl ring. All the NMR mass spectra details were presented in supplementary information.† The yield and results of the synthesized β-lactam fused polycyclicisoxazolidines were summarized in Table 3**.**

Table 3: Synthesis of β-lactam fused polycyclic isoxazolidine derivatives in ACI/EG RTIL medium through intermolecular 1,3-dipolar cycloaddition methodology

Entry	β-lactam nitrone	BH dipolarophile	β-lactam fused polycyclicisoxazolidines[a,b]	Yield (%)[c]
1.	**3a**	**5a**	**9a**	92
2.	**3a**	**5b**	**9b**	88
3.	**3a**	**5c**	**9c**	90
4.	**3a**	**6a**	**11a**	93
5.	**3a**	**6b**	**11b**	95
6.	**3a**	**6c**	**11c**	92
7.	**3a**	**7a**	**13a**	91
8.	**3a**	**7b**	**13b**	90
9.	**3a**	**7c**	**13c**	92
10.	**3a**	**8a**	**15a**	88
11.	**3a**	**8b**	**15b**	90
12.	**3a**	**8c**	**15c**	88

[a] Reaction conditions: Stirring at rt in ACI/EG RTIL medium.
[b] Completion of the reaction monitored by TLC.
[c] Yield of the isolated product after flash column chromatography.

3. Conclusion

In conclusion, highly regioselective polyfunctionalized β-lactam fused isoxazolidine heterocyclic hybrids were synthesized by 1,3-dipolar nitrone cycloaddition of β-lactam fused bicyclic nitrone with hydroxy allylic alkene derived from BH reaction and were economically achieved in RTIL medium. Comparing the yield and reactivity in organic solvents medium, it is clear that the high regioselectivity with shorter reaction time in

eco-friendly RTIL ACI/EG medium in room temperature plays a role. ACI/EG RTIL medium has never been used previously for cycloaddition reactions and it is reported for first time, showing remarkable reaction rate and selectivity even in hydroxy allylic dipolarophile. This ionic liquid medium offers high synthetic scope for the synthesis of highly regioselective novel class of bifunctional fused heterocycles. Also, recycling of ACI/EG has proved the ionic liquid's activity and selectivity.

4. Experimental

4.1. General information

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on BRUKER 300 MHz, mass spectra were recorded on JEOL- DX303 HF mass spectrometer and BRUKER DALTONICS FLEX Analysis spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400B instrument. Column chromatography was performed on silica gel (ACME, 100-200 mesh). Routine monitoring of the reactions was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness and visualized with iodine. After purification, all compounds were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, 2D-NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, DEPT-135).

4.2. General Procedure for the Synthesis of 2-azetidinone-tethered oximes, 2

Hydroxylamine hydrochloride (2.00 mmol) and triethylamine (2.00 mmol) were sequentially added at room temperature to a well stirred solution of the corresponding 4-oxoazetidine-2-carbaldehyde **1** (1.00 mmol) in benzene (10 mL). After the resulting suspension was stirred at room temperature overnight, the solvent was removed under reduced pressure. Then, the mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$ and then water. The combined organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate gave analytically pure compound **2**.

4.3. General Procedure for the Synthesis of Bicyclic Nitrones, 3a

Phenylselenyl bromide (1.00 mmol) was added at room temperature to a well stirred solution of the β–lactam oxime **2** (1.00 mmol) in dichloromethane (20 mL).

After the resulting suspension was stirred at room temperature for 3 h, triethylamine (1.00 mmol) was added and the mixture was stirred for an additional 1 h. The solvent was removed under reduced pressure. Then, the mixture was diluted with dichloromethane and washed with brine and water. The organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:3) mixture gave analytically pure compounds bicyclic nitrones **3a.**

4.4. General procedure for the synthesis of dipolarophiles, 5a-c to 8a-c

To a stirred solution of diketone / triketone (1.0 mmol) and corresponding acrylate (2.0 mL) was added DABCO (0.1 mmol) and stirred 50-60 °C for 60 min – 180 min. After completing the reaction evidenced by TLC, reaction mixture was diluted with dichloromethane and water. The organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (hexane/ethyl acetate, 1:1), we could obtain the desired dipolarophiles **5a-c** to **8a-c** in good yield.

4.5. General procedure for the synthesis of cycloadducts, 9a–c

The bicyclic nitrone **(3a)** (500 mg, 1.25 mmol) and BH adduct, 2,3-dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl)acrylates **(5a–c)** (306 mg, 1.25 mmol) was added in ACI/EG (10 mL) RTIL medium at room temperature and then stirred another 1 h. After completion of the reaction, evident by TLC, ionic liquid was distilled off under reduced pressure. 10 – 20 mL of chloroform was added in the residue and stirred for another 10–15 min. The organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and then crude cycloadducts were purified by flash column chromatography using hexane/ethyl acetate mixture (8:2). The purified isoxazolidines (**9a-c**) were subjected to spectroscopy analysis for structure determination.

4.5.1. 6-(1-Hydroxyindane-2,3-dione-1-yl)-6-methoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **9a**.
(92%); Colorless solid, mp 118-120 °C; FTIR (KBr) 3245, 1753, 1742, 1726, 1705 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 2.15 (s, 1H), 2.40-2.48 (m, 1H, H_{d1}), 2.70-2.79 (m, 1H,

H_{d2}), 3.69 (s, 3H), 3.76 (s, 3H, OMe), 3.70-3.75 (m, 2H, $PhSeCH_2$), 3.77-3.83 (m, 1H, H_a), 3.86-3.89 (m, 1H, H_c), 3.92-3.96 (m, 1H, H_e), 4.60-4.64 (m, 1H, H_b), 6.88-8.06 (m, 13H, ArH); ^{13}C (75 MHz, $CDCl_3$) 29.8, 34.5, 55.4, 59.1, 60.8, 63.4, 64.1, 66.8, 85.8, 114.4, 117.3, 123.5, 127.5, 129.4, 131.1, 132.8, 135.4, 135.9, 140.8, 143.1, 156.1, 164.5, 169.2, 194.4, 197.7 ppm; EI-MS *m/z* 647.53 (M^+). Anal. Calcd for $C_{32}H_{28}N_2O_8Se$: C, 59.35; H, 4.36; N, 4.33 %. Found: C, 59.48; H, 4.48; N, 4.25 %.

4.5.2. 6-(1-Hydroxyindane-2,3-dione-1-yl)-6-ethoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **9b**. (88%); Colorless solid, mp 126-128 °C; FT-IR (KBr) 3250, 1755, 1740, 1726, 1703 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* 7.2, 7.5 Hz, $COOCH_2CH_3$), 2.17 (s, 1H), 2.43-2.50 (m, 1H, H_{d1}), 2.74-2.80 (m, 1H, H_{d2}), 3.67-3.72 (m, 2H, $PhSeCH_2$), 3.77 (s, 3H, OMe), 3.78-3.86 (m, 1H, H_a), 3.89-3.91 (m, 1H, H_c), 3.92-3.94 (m, 1H, H_e), 4.12 (q, 2H, *J* 6.9, 6.9 Hz, $COOCH_2CH_3$), 4.59-4.62 (m, 1H, H_b), 6.81-7.98 (m, 13H, ArH); ^{13}C (75 MHz, $CDCl_3$) 13.6, 29.9, 34.5, 55.4, 59.1, 60.8, 63.4, 64.1, 66.8, 85.8, 114.4, 117.3, 123.5, 127.5, 129.4, 131.1, 132.9, 135.3, 135.9, 140.9, 143.0, 156.1, 164.5, 168.9, 194.4, 197.6 ppm; EI-MS *m/z* 661.56 (M^+). Anal. Calcd for $C_{33}H_{30}N_2O_8Se$: C, 59.91; H, 4.57; N, 4.23 %. Found: C, 60.02; H, 4.66; N, 4.11 %.

4.5.3. 6-(1-Hydroxyindane-2,3-dione-1-yl)-6-cyano-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **9c**. (90%); Colorless solid, mp 122-124 °C; FTIR (KBr) 3242, 2223, 1754, 1739, 1706 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 2.19 (s, 1H), 2.46-2.53 (m, 1H, H_{d1}), 2.77-2.84 (m, 1H, H_{d2}), 3.66-3.70 (m, 2H, $PhSeCH_2$), 3.79 (s, 3H, OMe), 3.80-3.88 (m, 1H, H_a), 3.90-3.92 (m, 1H, H_c), 3.91-3.94 (m, 1H, H_e), 4.58-4.62 (m, 1H, H_b), 6.86-8.14 (m, 13H, ArH); ^{13}C (75 MHz, $CDCl_3$) 29.9, 34.5, 55.5, 59.2, 63.4, 64.1, 66.9, 85.9, 114.6, 117.4, 120.1, 123.5, 127.5, 129.6, 131.1, 132.8, 135.4, 135.4, 140.9, 143.2, 156.1, 164.4, 194.4,197.6 ppm; EI-MS *m/z* 614.51 (M^+). Anal. Calcd for $C_{31}H_{25}N_3O_6Se$: C, 60.59; H, 4.10; N, 6.84 %. Found: C, 60.68; H, 4.01; N, 6.98 %.

4.6. General procedure for the synthesis of cycloadducts, 11a-c

The bicyclic nitrone **(3a)** (500 mg, 1.25 mmol) and BH adduct, 2-(3-hydroxy-2-oxoindolin-3-yl)acrylates **(6a-c)** (290 mg, 1.25 mmol) was added in ACI/EG (10 mL)

RTIL medium at room temperature and then stirred another 1h. After completion of the reaction, evident by TLC, ionic liquid was distilled off under reduced pressure. 10 – 20 mL of chloroform was added in the residue and stirred for another 10–15 min. The organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and then crude cycloadducts were purified by flash column chromatography using hexane/ethyl acetate mixture (8:2). The purified isoxazolidines (**11a-c**) were subjected to spectroscopy analysis for structure determination.

4.6.1. 6-(3-Hydroxyindolin-2-on-3-yl)-6-methoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **11a**. (93%); Colorless solid, mp 162-164 °C; FTIR (KBr) 3392, 1756, 1726, 1695 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 2.13 (s, 1H), 2.45-2.51 (m, 1H, H_{d1}), 2.75-2.81 (m, 1H, H_{d2}), 3.67 (s, 3H), 3.68-3.72 (m, 2H, $PhSeCH_2$), 3.74 (s, 3H, OMe), 3.75-3.76 (m, 1H, H_a), 3.90-3.93 (m, 1H, H_c), 3.95-3.97 (m, 1H, H_e), 4.60-4.62 (m, 1H, H_b), 6.81-7.97 (m, 13H, ArH), 9.11 (s, 1H, *N*H); ^{13}C (75 MHz, $CDCl_3$) 30.1, 33.5, 54.4, 59.1, 60.8, 63.4, 64.1, 67.4, 86.9, 108.6, 113.4, 118.4, 122.6, 128.6, 130.5, 131.6, 137.7, 139.2, 139.9, 143.1, 156.2, 164.5, 169.5, 178.1 ppm; EI-MS *m/z* 634.54 (M^+). Anal. Calcd for $C_{31}H_{29}N_3O_7Se$: C, 58.68; H, 4.61; N, 6.62 %. Found: C, 58.80; H, 4.70; N, 6.68 %.

4.6.2. 6-(3-Hydroxyindolin-2-on-3-yl)-6-ethoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **11b**. (95%); Colorless solid, mp 186-188 °C; FTIR (KBr) 3384, 1752, 1728, 1691 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 0.85 (t, 3H, *J* 7.5, 7.5 Hz, $COOCH_2CH_3$), 2.15 (s, 1H), 2.39-2.43 (m, 1H, H_{d1}), 2.69-2.75 (m, 1H, H_{d2}), 3.68-3.75 (m, 2H, $PhSeCH_2$), 3.81 (s, 3H, OMe), 3.83-3.87 (m, 1H, H_a), 3.91-3.95 (m, 1H, H_c), 3.96-3.98 (m, 1H, H_e), 4.12 (q, 2H, *J* 7.2, 6.9 Hz, $COOCH_2CH_3$), 4.53-4.58 (m, 1H, H_b), 6.73-7.86 (m, 13H, ArH), 9.16 (s, 1H, *N*H); ^{13}C (75 MHz, $CDCl_3$) 12.9, 30.6, 33.3, 54.9, 59.1, 60.9, 63.4, 64.5, 66.8, 86.6, 109.0, 113.9, 117.3, 123.6, 127.9, 129.4, 131.4, 135.3, 137.9, 140.5, 143.2, 156.2, 164.4, 169.7, 178.2 ppm; EI-MS *m/z* 648.56 (M^+). Anal. Calcd for $C_{32}H_{31}N_3O_7Se$: C, 59.26; H, 4.82; N, 6.48 %. Found: C, 59.38; H, 4.91; N, 6.59 %.

4.6.3. 6-(3-Hydroxyindolin-2-on-3-yl)-6-cyano-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **11c**. (92%); Colorless solid, mp 132-134 °C; FTIR (KBr) 3384, 2223, 1753, 1693 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 2.18 (s, 1H), 2.43-2.51 (m, 1H, H_{d1}), 2.76-2.82 (m, 1H, H_{d2}), 3.65-3.72 (m, 2H, $PhSeCH_2$), 3.76 (s, 3H, OMe), 3.78-3.81 (m, 1H, H_a), 3.86-3.89 (m, 1H, H_c), 3.90-3.93 (m, 1H, H_e), 4.55-4.58 (m, 1H, H_b), 6.79-7.98 (m, 13H, ArH), 9.16 (s, 1H, *N*H); ^{13}C (75 MHz, $CDCl_3$) 28.7, 33.5, 55.5, 59.1, 63.4, 64.2, 66.8, 85.9, 109.9, 114.6, 117.3, 120.1, 123.5, 127.5, 129.6, 131.1, 132.8, 135.3, 135.4, 140.9, 143.2, 156.1, 164.5, 178.2 ppm; EI-MS *m/z* 601.51 (M^+). Anal. Calcd for $C_{30}H_{26}N_4O_5Se$: C, 59.90; H, 4.36; N, 9.31 %. Found: C, 59.81; H, 4.48; N, 9.39 %.

4.7. General procedure for the synthesis of cycloadducts, 13a-c

The bicyclic nitrone **(3a)** (500 mg, 1.25 mmol) and BH adduct, 2-(1,2-dihydro-1-hydroxy-2-oxoacenaphthylen-1-yl) acrylates **(7a-c)** (335 mg, 1.25 mol) was added in ACI/EG (10 mL) RTIL medium at room temperature and then stirred another 1h. After completion of the reaction, evident by TLC, ionic liquid was distilled off under reduced pressure. 10 – 20 mL of chloroform was added in the residue and stirred for another 10–15 min. The organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and then crude cycloadducts were purified by flash column chromatography using hexane/ethyl acetate mixture (8:2). The purified isoxazolidines (**13a-c**) were subjected to spectroscopy analysis for structure determination.

4.7.1. 6-(2-Hydroxyacenaphthen-1-on-2-yl)-6-methoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **13a**. (91%); Colorless solid, mp 242-244 °C; FTIR (KBr), 1756, 1695 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 2.12 (s, 1H), 2.41-2.52 (m, 1H, H_{d1}), 2.71-2.79 (m, 1H, H_{d2}), 3.62 (s, 3H), 3.67-3.73 (m, 2H, $PhSeCH_2$), 3.74-3.77 (m, 1H, H_a), 3.78 (s, 3H, OMe), 3.90-3.94 (m, 1H, H_c), 3.95-3.98 (m, 1H, H_e), 4.58-4.61 (m, 1H, H_b), 6.83-8.15 (m, 15H, ArH); ^{13}C (75 MHz, $CDCl_3$) 28.6, 31.3, 55.5, 59.2, 63.4, 64.0, 66.6, 88.6, 105.3, 114.5, 120.6, 121.1, 122.9, 123.5, 124.6, 126.7, 127.7, 128.3, 128.5, 129.6, 130.9, 131.1, 134.2, 135.3, 137.2, 141.6, 156.2, 164.5, 201.5 ppm; EI-MS *m/z* 669.58 (M^+). Anal. Calcd. for $C_{35}H_{30}N_2O_7Se$: C, 62.78; H, 4.52; N, 4.18 %. Found: C, 62.89; H, 4.61; N, 4.26 %.

4.7.2. 6-(2-Hydroxyacenaphthen-1-on-2-yl)-6-ethoxycarbonyl-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **13b**. (90%); Colorless solid, mp 226-228 °C; FTIR (KBr), 1752, 1691 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* 7.2, 7.5 Hz, $COOCH_2CH_3$), 2.13 (s, 1H), 2.38-2.43 (m, 1H, H_{d1}), 2.67-2.73 (m, 1H, H_{d2}), 3.68-3.72 (m, 2H, $PhSeCH_2$), 3.80 (s, 3H, OMe), 3.77-3.82 (m, 1H, H_a), 3.90-3.93 (m, 1H, H_c), 3.96-3.99 (m, 1H, H_e), 4.01 (q, 2H, *J* 7.2, 7.2 Hz, $COOCH_2CH_3$), 4.57-4.64 (m, 1H, H_b), 6.86-8.19 (m, 15H, ArH); ^{13}C (75 MHz, $CDCl_3$) 12.6, 28.5, 31.3, 55.5, 59.2, 63.4, 64.0, 66.6, 88.6, 105.3, 114.5, 120.6, 121.0, 123.3, 124.5, 126.7, 127.8, 128.3, 128.6, 129.6, 130.9, 131.1, 134.2, 135.3, 137.2, 141.6, 156.2, 164.5, 201.6 ppm; EI-MS *m/z* 683.61 (M^+). Anal. Calcd. for $C_{36}H_{32}N_2O_7Se$: C, 63.25; H, 4.72; N, 4.10 %. Found: C, 63.33; H, 4.61; N, 4.18 %.

4.7.3. 6-(2-Hydroxyacenaphthen-1-on-2-yl)-6-cyano-1-(4-methoxyphenyl)-3-(phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **13c**. (92%); Colorless solid, mp 210-112 °C; FTIR (KBr) 2118, 1751, 1706 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 2.15 (s, 1H), 2.39-2.45 (m, 1H, H_{d1}), 2.73-2.81 (m, 1H, H_{d2}), 3.68-3.75 (m, 2H, $PhSeCH_2$), 3.76-3.79 (m, 1H, H_a), 3.80 (s, 3H, OMe), 3.91-3.95 (m, 1H, H_c), 3.96-3.99 (m, 1H, H_e), 4.59-4.65 (m, 1H, H_b), 6.88-8.16 (m, 15H, ArH); ^{13}C (75 MHz, $CDCl_3$) 29.6, 30.3, 55.5, 59.2, 63.4, 64.0, 66.6, 88.6, 105.3, 114.5, 120.6, 121.0, 122.9, 123.5, 124.6, 126.7, 127.8, 128.3, 128.5, 129.6, 130.9, 131.1, 134.2, 135.3, 137.2, 141.6, 156.2, 164.5, 201.5 ppm; EI-MS *m/z* 636.56 (M^+). Anal. Calcd for $C_{34}H_{27}N_3O_5Se$: C, 64.15; H, 4.28; N, 6.60 %. Found: C, 64.27; H, 4.37; N, 6.51 %.

4.8. General procedure for the synthesis of cycloadducts, 15a-c

The bicyclic nitrone **(3a)** (500 mg, 1.25 mmol) and bis-BH adduct, 2-(1,2-dihydro-1-hydroxy-2-oxoacenaphthylen-1-yl) acrylates **(8a-c)** (180 mg, 0.05 mmol) was added in ACI/EG (10 mL) RTIL medium at room temperature and then stirred another 1h. After completion of the reaction, evident by TLC, ionic liquid was distilled off under reduced pressure. 10 – 20 mL of chloroform was added in the residue and stirred for another 10–15 min. The organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and then crude cycloadducts were purified by flash column chromatography using hexane/ethyl

acetate mixture (7:3). The purified isoxazolidines (**15a-c**) were subjected to spectroscopy analysis for structure determination.

4.8.1. 6-[1,4-Phenylenebis(hydroxymethyl-1-yl)]-6,6'-bi(methoxycarbonyl)-1-(4-methoxyphenyl)- 3- (phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b] isoxazol-2-one, **15a**. (88%); Colorless solid, mp 222-224 °C; FTIR (KBr) 3200, 2128, 1753 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 2.17 (s, 2H), 2.49-2.56 (m, 2H, H_{d1}), 2.72-2.79 (m, 2H, H_{d2}), 2.97-3.12 (m, 4H, $PhSeCH_2$), 3.30 (s, 6H, COOMe), 3.76 (s, 6H, OMe), 3.79-3.81 (m, 2H, H_a), 4.08-4.10 (m, 2H, H_c), 4.32-4.35 (m, 2H, H_e), 4.49-4.51 (m, 2H, H_b), 5.03 (s, 2H, benzylicproton), 6.69-7.59 (m, 22H, ArH); ^{13}C (75 MHz, $CDCl_3$) 30.6, 32.7, 52.5, 55.3, 55.4, 57.0, 59.6, 63.3, 64.6, 90.2, 114.2, 114.4, 117.2, 126.5, 126.6, 126.9, 127.5, 129.3, 131.1, 133.2, 133.3, 137.8, 156.1, 164.4, 170.1 ppm; MALDI-TOF *m/z* 1108.97 (M^+). Anal. Calcd for $C_{54}H_{54}N_4O_{12}Se_2$: C, 58.49; H, 4.91; N, 5.05 %. Found: C, 58.58; H, 4.80; N, 5.16 %.

4.8.2. 6-[1,4-Phenylenebis(hydroxymethyl-1-yl)]-6,6'-bi(ethoxycarbonyl)-1-(4-methoxyphenyl)-3- (phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b] isoxazol-2-one, **15b**. (90%); Colorless solid, mp 254-256 °C; FTIR (KBr) 3235, 2122, 1755 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 0.82 (t, 3H, *J* 7.2, 6.9 Hz, $COOCH_2CH_3$), 2.18 (s, 2H), 2.50-2.56 (m, 2H, H_{d1}), 2.73-2.81 (m, 2H, H_{d2}), 2.98-3.12 (m, 4H, $PhSeCH_2$), 3.79 (s, 6H, OMe), 3.80-3.83 (m, 2H, H_a), 3.96 (dq, 4H, *J* 6.9, 7.5 Hz, $COO\underline{CH_2}CH_3$), 4.10-4.13 (m, 2H, H_c), 4.34-4.36 (m, 2H, H_e), 4.39-4.43 (m, 2H, H_b), 5.11 (s, 2H, benzylicproton), 6.71-7.82 (m, 22H, ArH); ^{13}C (75 MHz, $CDCl_3$) 13.7, 30.6, 29.8, 33.9, 55.3, 55.8, 57.1, 59.6, 63.3, 64.6, 90.2, 114.2, 114.5, 117.2, 126.5, 126.6, 126.9, 127.5, 129.3, 131.1, 133.3, 133.5, 137.7, 156.1, 164.4, 171.0 ppm; MALDI-TOF *m/z* 1137.03 (M^+). Anal. Calcd for $C_{56}H_{58}N_4O_{12}Se_2$: C, 59.16; H, 5.14; N, 4.93 %. Found: C, 59.25; H, 5.22; N, 5.01 %.

4.8.3. 6-[1,4-Phenylenebis(hydroxymethyl-1-yl)]-6,6'-bi(cyano)-1-(4-methoxyphenyl)-3- (phenylselenenylmethyl)octahydroazeto[2',3':3,4]pyrrolo[1,2-b]isoxazol-2-one, **15c**. (88%); Colorless solid, mp 228-230 °C; FTIR (KBr) 3218, 2123, 1755 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 2.17 (s, 2H), 2.51-2.57 (m, 2H, H_{d1}), 2.87-2.95 (m, 2H, H_{d2}), 2.98-3.12 (m, 4H, $PhSeCH_2$), 3.74 (s, 6H, OMe), 3.85-3.87 (m, 2H, H_a), 4.10-4.14 (m, 2H, H_c),

4.24-4.25 (m, 2H, H_e), 4.68-4.72 (m, 2H, H_b), 5.10 (s, 2H, benzylic proton), 6.82-7.87 (m, 22H, ArH); ^{13}C (75 MHz, $CDCl_3$) 30.5, 30.8, 35.8, 55.4, 57.1, 59.8, 63.6, 65.6, 80.9, 114.6, 117.8, 127.8, 127.9, 129.0, 129.5, 129.6, 130.5, 133.3, 136.7, 142.4, 156.5, 163.8 ppm; MALDI-TOF *m/z* 1042.88 (M^+). Anal. Calcd for $C_{52}H_{48}N_6O_8Se_2$: C, 59.89; H, 4.64; N, 8.06 %. Found: C, 59.98; H, 4.72; N, 8.13 %.

Acknowledgement

Authors acknowledge the support by the Deanship of Scientific Research, College of Science Research Centre at King Saud University.

Supplementary data

† Supplementary data (NMR, MALDI-TOF spectra of representative compounds are given in supplementary information material).

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