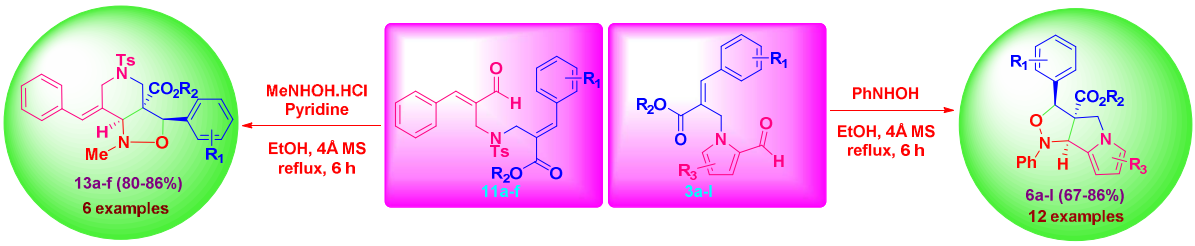
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

A Facile Synthesis of Isoxazolo[3,4-a]pyrrolizine and Isoxazolo[4,3-c]pyridine Derivatives via Intramolecular Nitrone Cycloaddition Reaction

Manickam Bakthadoss,[a,b*] Jayakumar Srinivasan[b]
[a]*Department of Chemistry, Pondicherry University, Pondicherry-605014, India*
[b]*Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600025, Tamil Nadu, India*
Fax: 91-413-2654830; E-mail: bhakthadoss@yahoo.com



A facile and efficient protocol for the construction of isoxazolo[3,4-a]pyrrolizine and isoxazolo[4,3-c]pyridine derivatives through *in situ* formation of nitrone ylide followed by an intramolecular [3+2] cycloaddition reaction is described. This reaction paved the pathway way for the successful assembly of an angularly substituted cyclic heterocycles, which creats two new rings, three contiguous stereocentres and one tetra substituted carbon center in a highly diastereoselective fashion with good yields.

Journal Name

COMMUNICATION

A Facile Synthesis of Isoxazolo[3,4-a]pyrrolizine and Isoxazolo[4,3-c]pyridine Derivatives via Intramolecular Nitrone Cycloaddition Reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Manickam Bakthadoss,[a,b]* Jayakumar Srinivasan[b]

A facile and efficient protocol for the construction of isoxazolo[3,4-a]pyrrolizine and isoxazolo[4,3-c]pyridine derivatives through *in situ* formation of nitrone ylide followed by an intramolecular [3+2] cycloaddition reaction is described. This reaction paved the pathway way for the successful assembly of an angularly substituted cyclic heterocycles, which creats two new rings, three contiguous stereocentres and one tetra substituted carbon center in a highly diastereoselective fashion with good yields.

The development of highly efficient strategies for the synthesis of isoxazolidines is very important since isoxazolidines represent an important class of versatile intermediates for a wide range of natural products and pharmaceuticals. Notably, these five-membered ring heterocycles can readily be converted into numerous useful functional groups such as amino acids, β-lactams, and 1,3-amino alcohols through reductive N–O bond cleavage. Therefore, it is not surprising that great efforts have been devoted to the development of new methods for the construction of isoxazolidine core. Among the different approaches available for the preparation of this structural motifs, [3 + 2] cycloaddition of nitrones with alkenes is one of the most straightforward and convenient method[1] which leads to interesting structural units.

Naturally-occurring pyrrole alkaloids and their derivatives have attracted significant attentions due to their bioactivities such as antibacterial activity and antimicrobial activities.[2] important representatives of the naturally-occurring pyrrole fused tricylic alkaloids such as Phakellstatin (**I**), Dibromoagelaspongin (**II**) and Agelastatin B (**III**) are shown in Figure 1.[3] Similarly, piperidine derivatives are very important in synthetic and medicinal chemistry due to their occurrence in numerous biologically relevant alkaloids and pharmaceutical agents.[4] Typical examples include antibiotic and anesthetic prosopis alkaloid prosophylline (**IV**), α-Skytanthine (**V**) and Tecomanine (**VI**) which displays a variety of biological activities including neurogenic inflammation, pain transmission, and regulation of the immune response (Figure 1).[5]

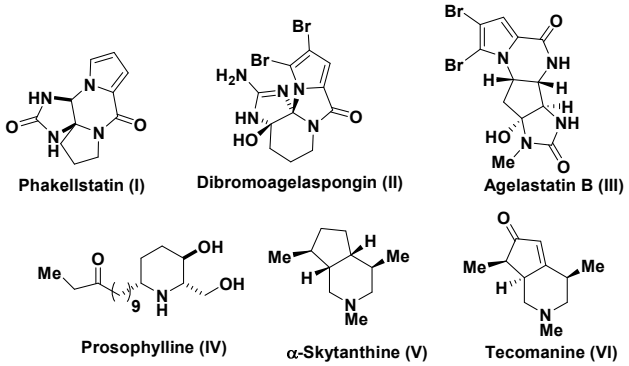
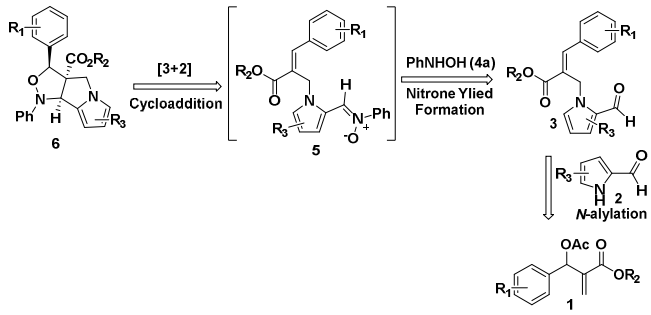


Figure 1. Some of the natural products embodying pyrrole and piperidine units

To the best of our knowledge[6], the Baylis-Hillman derivatives have not been utilized for the synthesis of fused tricyclic tetrahydro-1*H*-isoxazolo[3,4-*a*]pyrrolizine and octahydro isoxazolo[4,3-*c*]pyridine *via* 1,3-dipolar nitrone cycloaddition to date. Therefore, In our continuous effort towards the synthesis of highly functionalized poly heterocyclic compounds[7], we speculated that the Baylis-Hillman derivatives can be effectively employed as a key starting material for the synthesis of complex angularly substituted tetrahydro-1*H*-isoxazolo[3,4-a]pyrrolizine and octahydroisoxazolo [4,3-c]pyridine frameworks *via* intramolecular 1,3-dipolar nitrone cycloaddition reaction.

We envisaged that treatment of Baylis-Hillman acetate (**1**) with pyrrole-2-carboxaldehyde (**2**) will leads to (*E*)-methyl 2-((2-formyl-1*H*-pyrrol-1-yl)methyl)-3-phenylacrylate (**3**) and further treatment of *N*-allylated aldehyde (**3**) with *N*-phenylhydroxylamine (**4**) will afford the tricyclic tetrahydro-1*H*-isoxazolo[3,4-a]pyrrolizine (6) with ester functionality in the ring junction as depicted in the retrosynthetic strategy (Scheme 1).

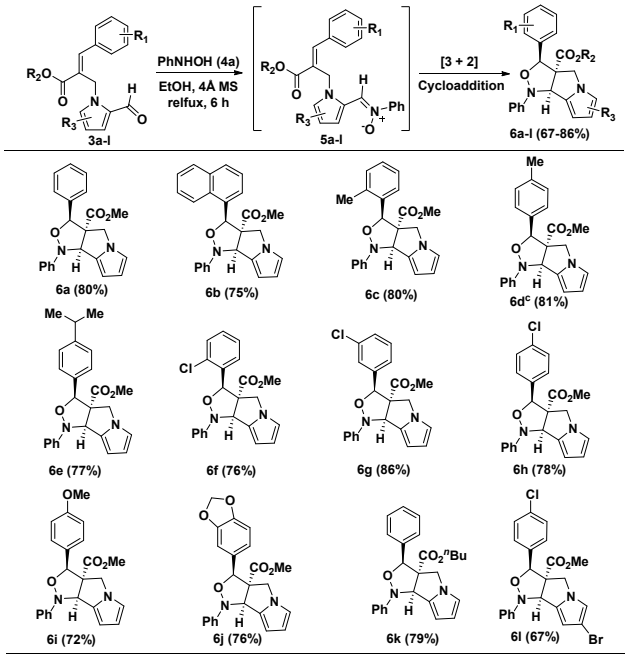
[a] *Department of Chemistry, Pondicherry University, Pondicherry - 605 014, India.*
[b] *Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600 025, Tamilnadu, India. bhakthadoss@yahoo.com.*
[c] *† All experimental procedure, spectral data and copies of ^{1}H and ^{13}C NMR spectra and of all new compounds, X-ray structural data for compounds 6d & 13f See DOI: 10.1039/x0xx00000x*



Scheme 1. Retrosynthetic Strategy for the Synthesis of isoxazolo[3,4-*a*]pyrrolizine.

To execute our idea we treated *N*-allylated aldehyde **3a** (prepared from BH acetate with **2**) and PhNHOH (**4a**) with 4Å MS in ethanol as solvent under reflux condition over a period of 6 h which successfully led to the desired isoxazolo[3,4-*a*]pyrrolizine (**6a**) containing ester functionality at the angular position in very good yield (80%). The reaction proceeds through an in situ formation of nitrone (**5a**) followed by [3+2] cycloaddition reaction sequence as shown in Table 1.

Table 1. Synthesis of tricyclic isoxazolo[3,4-a]pyrrolizine Frameworks (**6a-l**)[a,b] with Ester Functionality at Angular Position.



[a]All reactions were carried out on 1 mmol scale of *N*-allylated derivatives (**3a-l**) with 1.1 mmol of PhNHOH (**4a**) with 4Å MS in EtOH (10 mL) as a solvent at reflux temperature for 6h. [b] Isolated yield of the pure product. [c]Structure of the molecule was further confirmed by single-crystal X-ray data.[8]

Encouraged by this result, we have utilized variety of *N*-allylated aldehydes (**3b-l**), with PhNHOH (**4a**) under similar reaction condition which smoothly led to the corresponding tricyclic tetrahydro-1H-isoxazolo[3,4-a]pyrrolizines (**6b-l**) possessing ester functionality at the angular position in good yields (67-86%) and the results are summarized in Table 1. Brominated pyrrole derivative (**3l**) also utilized for cycloaddition reaction and provided the corresponding cycloadduct **6l** (67% yield) which will be useful for further elaboration in pyrrole unit. The structure of the molecule **6d** was confirmed using single crystal X-ray analysis. The crystal structure of compound **6d** shows that the phenyl group and the adjacent ester moiety adopt an anti-orientation, which is presumably due to the initial trans geometry of the phenyl group and ester moiety present in the double bond at the vicinal positions of compound **3d** (Figure 2). The ring junction ester and hydrogen are in *cis* orientation.

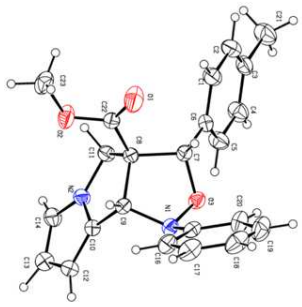
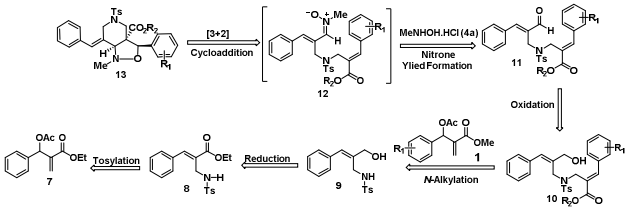


Figure 2. ORTEP diagram of compound **6d**

After the successful synthesis of tetrahydro-1*H*-isoxazolo[3,4-a]pyrrolizine frameworks, we focussed our attention towards the synthesis of octahydroisoxazolo[4,3-c]pyridine derivatives from the MBH adducts of acrylates which will undergo intramolecular nitrone cycloaddition to furnish isoxazolo[4,3-c]pyridine (**13**) as shown in the retrosynthetic strategy (Scheme 2).

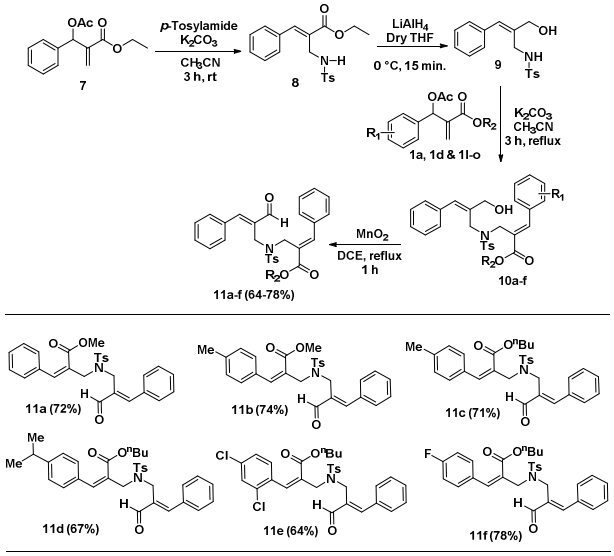


Scheme 2. Retrosynthetic Strategy for the Synthesis of isoxazolo[4,3-*c*]pyridine derivatives.

The approach for the synthesis of isoxazolo[4,3-*c*]pyridine (**13**) involves the utilization of BH acetate **7**, which was transformed to allylamine **8** in a stereo selective fashion *via* SN_2' reaction with tosylamine in the presence of K_2CO_3 in CH_3CN for 3h at room temperature. In order to reduce the ester functionality into alcohol group, allylamine **8** was treated with $LiAlH_4$ in THF at 0 °C for 15 minutes which afforded the corresponding alcohol **9**. The reaction of substituted alcohol **9** with BH acetates (**1**) in the presence of K_2CO_3 in CH_3CN at reflux temperature for 3 h afforded allylic alcohol **10a** in a chemo selective fashion. Further oxidation of allylic alcohol **10a** in presence of MnO_2 afforded the aldehyde compound **11a** in 72% yield (Table 2). After successfully obtained the requisite aldehyde **11a,** we prepared variety of aldehyde derivatives **11b-f** in

good yields (64-78%) with a view to carry out the nitrone cycloaddition reaction.

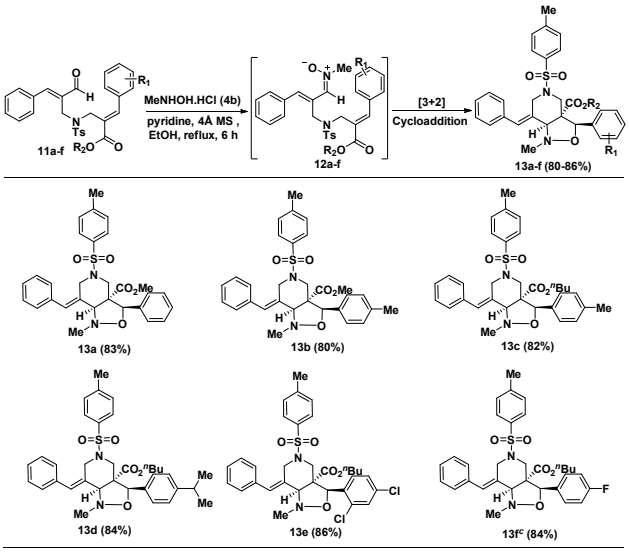
Table 2. Synthesis of (*E*)-methyl 2-((*N*-((*E*)-2-formyl-3-phenylallyl)-4-methylphenylsulfonamido)methyl)-3-arylacrylates (**11a-f**).[a,b]



[a]All reactions were carried out on 1 mmol scale of allylic alcohol (**10a-f**) with 2 mmol of MnO_2 in DCE (20 mL) as a solvent at reflux temperature for 1 h. [b] Isolated yield of the pure product.

In order to synthesize the cycloadduct **13a**, the requisite precursor **11a** was treated with *N*-methylhydroxylamine hydrochloride (**4b**) in the presence of pyridine as a base with 4Å MS

Table 3. Synthesis of isoxazolo[4,3-c]pyridine (**13a-f**)[a,b] Ester Functionality at Angular Substitution.



[a]All reactions were carried out on 1 mmol scale of aldehydes (**11a-f**) with 1.1 mmol of MeNHOH.HCl (**4b**) presence of pyridine with 4Å MS in allowed to stir in EtOH (10 mL) at reflux temperature for 6 h. [b]Isolated yields of the pure product. [c]The structure of the molecule was further confirmed by single-crystal X-ray data.[8]

in ethanol under reflux condition for 6 h afforded a desired product **13a** in 83% yield. Encouraged by the result, we carried out the cycloaddition reaction of substrates **11b-f** with *N*-methyl hydroxylamine hydrochloride (**4b**) successfully afforded a desired isoxazolo[4,3-c]pyridines (**13b-f**) in 80-86% yields (Table 3). The structure of the compound **13f** was further confirmed using single crystal X-ray analysis (Figure 2).

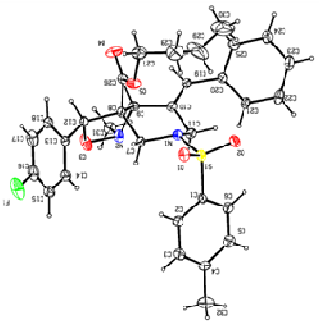
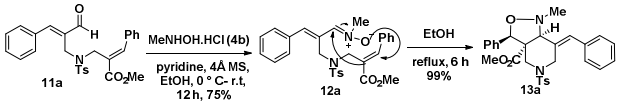


Figure 2. ORTEP diagram of compound **13f**

We believe that the reaction proceeds via the formation of nitrone followed by intramolecular [3 + 2] cycloaddition reaction. To confirm the intermediate, we have isolated the nitrone intermediate (75%) by following the reaction condition depicted in Scheme 3. The nitrone intermediate **12a** was refluxed in EtOH for 6 h which successfully led to the desired cycloadduct **13a** in 99% yield.



Scheme 3: Plausible mechanism for the formation of isoxazolo[4,3-c]pyridine.

Conclusions

We have successfully developed a simple and novel protocol for the facile synthesis of complex angularly substituted frameworks containing a Isoxazolo[3,4-a]pyrrolizine and Isoxazolo[4,3-c]pyridine ring system involving *in situ* formation of nitrone followed by an intramolecular 1, 3-dipolar nitrone cycloaddition reaction using Baylis-Hillman derivatives for the first time. The new [3 + 2] cycloaddition reaction leads to a novel class of angularly substituted fused bicyclic/tricyclic Isoxazolo[4,3-c]pyridine and Isoxazolo[3,4-a]pyrrolizine, creating two rings, three contiguous stereocentres, one of them being a tetra substituted carbon center in a unique fashion.

Notes and references

(1) Jones, R. C. F.; Martin, J. N. I*n Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp 1–81.

(2) (a) Cafieri, F.; Fattorusso, E.; Tagliatatela-Scafati, O. *J. Nat. Prod.* 1998, 61, 122. (b) Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Tagliatatela-Scafati, O.; Vallefuoco, T. *Bioorg. Med. Chem. Lett.* 1997, **7**, 2283.

(3) (a) Pettit, G. P.; McNulty, J.; Herald, L.; Doubek, D. L.; Chapuis, J-C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. P. *J. Nat. Prod.* 1997, **60**,180. (b) Wang, S. Romo, D. *Angew. Chem. Int. Ed.* 2008, **47**, 1284. (c) Jin, Z. *Nat. Prod. Rep.,* 2011, **28**, 1143.

(4) (a) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem*. 2004, **69**, 6001. (b) Vidyacharan, S.; Shinde, A. H.; Satpathi, B.; Sharada, D. S. *Green Chem*., 2014, **16**, 1168 (c) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett*. 2006, **47**, 5317. (d) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* 2008, **10**, 4335. (e) Prévost, S.; Phansavath, P.; Haddad, M. *Tetrahedron: Asymmetry* 2010, **21**, 16. (f) Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q. *Org. Lett.* 2011, **13**, 4938. (g) Tan, C. K.; Le, C.; Yeung, Y.-Y. *Chem. Commun.* 2012, **48**, 5793. (h) Pansare, S. V.; Paul, E. K. *Org. Biomol. Chem.* 2012, **10**, 2119. (i) Vidyacharan, S.; Sagar, A.; Chaitra, C.; Sharada, D. S. *RSC Adv*. 2014, **4**, 34232.

(5) (a) Ma, X. Q.; Gang, D. R. *Nat. Prod. Rep.* 2004, **21**, 752. (b) Kaneda, K., Honda, T. *Tetrahedron* 2008, **64**, 11589. (c) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem*. 1992, **35**, 4911.

(6) (a) Beccalli, E. M.; Broggini, G.; Rosa, G, La.; Passarella, D.; Pilati, T. *J. Org. Chem.* 2000**, 65**, 8924. (b) Terraneo, A.; Zecchi, G.; Arnone, A.; Broggini, G.; Passarella, D.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* 1998**, 63**, 9279-9284. (c) Mishra, A.; Rastogi, N.; Batra, S. *Tetrahedron,* 2012, **68**, 2146.

(7) (a) Bakthadoss, M.; Kannan, D.; Srinivasan. J. Vinayagam, V. *Org. Biomol. Chem.* 2015, **13**, 2870. (b) Bakthadoss, M.; Kannan, D. *RSC Adv.* 2014, **4**, 11723. (c) Bakthadoss, M.; Sivakumar, G. *Tetrahedron Lett.* 2014, **55**, 1765. (d) Basavaiah, D.; Bakthadoss, M.; Jayapal Reddy, G. *Synth. Commun*. 2002, **32**, 689. (e) Bakthadoss, M.; Devaraj, A.; Kannan, D. *Eur. J. Org. Chem*. 2014, 1505. (f) Bakthadoss, M.; Kannan, D.; Selvakumar, R. *Chem. Commun*. 2013, **49**, 10947. (g) Bakthadoss, M.; Murugan, G. *Synth. Commun*. 2008, **38**, 3406. (h) Bakthadoss, M.; Srinivasan, J.; Selvakumar, R. *Aust. J. Chem*. 2014, **67**, 295. (i) Bakthadoss, M.; Sivakumar, G.; Sharada, D. S. *Synthesis,* 2013, 237-245. (j) Bakthadoss, M.; Murugan, G. Eur. J. Org. Chem 2010, 5825. (k) Bakthadoss, M.; Devaraj, A. *Tetrahedron Lett*. 2015, **56**, 3954.

(8) Structures were confirmed by single-crystal X-ray data, CCDC number for the compounds **6d** and **13f** have **1053095** & **1035588** respectively.

