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Microwave-assisted facile synthesis of [*a*]-annelated pyrazolopyrroloindoles via intramolecular azomethine imine 1,3-dipolar cycloaddition

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ABSTRACT

The synthesis of [*a*]-annelated pyrazolopyrroloindoles via intramolecular 1,3-dipolar cycloaddition of in situ generated azomethine imine from *N*-allylated indole-2-carboxaldehyde, in regio- and stereoselective manner by using microwave irradiation is described. A one-pot strategy for the expedient synthesis of pyrazolopyrroloindoles has been developed.

The chemistry of fused biheterocycles has been the fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile.[1] Heterocyclic compounds play an important role in medicinal chemistry and natural products. Among them, [*a*]-annelated indole is a unique structural feature, present in a wide range of heterocyclic compounds. Pyrrolo[1,2-*a*]-indole[2,3] scaffold is a primary target for synthetic chemists due to its structural diversity. The biological significance of these motifs has been clearly exemplified by natural products and synthetic compounds, such as flinderole C (**1**),[4] mitomycin C (**2**),[5] isatisine A (**3**),[6] yuremamine (**4**)[7] and so forth (Fig. 1). Owing to the importance of pyrroloindole scaffolds, there has been continuous interest to develop new synthetic methods such as N-heterocyclic carbene catalyzed domino reaction between 1*H*-indole-2-carbaldehydes and formylcyclopropane 1,1-diesters,[3b] nitrile oxide cycloaddition,[3c] palladium catalyzed cyclization,[3d–g] and radical cyclization.[3h]

1,3-Dipolar cycloaddition is one of the important methods for the synthesis of five-membered heterocyclic compounds in a regio- and stereocontrolled manner.[8] Five-membered heterocyclic compounds form an integral part of natural products and bioactive molecules, specifically pyrazoles are known to possess a broad spectrum of biological activities, such as anti-tumor, anti-inflammatory,[9] anti-microbial,[10] anti-anxiolytic,[11] herbicidal,[12a] and insecticidal activities.[12b] For instance Celecoxib (**6**), a pyrazole derivative is used as an analgesic. They have a rich chemistry because of their ready reductive cleavage[13] and susceptibility to ring transformations.[14] Among various literature methods,[15] 1,3-dipolar cycloaddition of azomethine imine is the well-known strategy for the synthesis of pyrazoles and its derivatives.[16] Azomethine imines are less common than other 1,3-dipoles but are known to react with alkene in inter-[17] or intramolecular[18] fashion to construct variety of ring-fused pyrazolidines.[19] Cyclic azomethine imines are widely explored dipoles in cycloaddition reactions with various dipolarophiles leading to a wide variety of pyrazole fused heterocyclic compounds. In contrast, acyclic azomethine imines have gained little attention due to requisite harsh reaction conditions. However, generation of stabilized acyclic azomethine imines has been facilitated by acid additives.[20]

Microwave-assisted organic synthesis (MAOS)[21] has become an effective and popular tool in synthetic chemistry due to advantages such as drastic acceleration of sluggish transformations, enhanced yields, cleaner reactions, and rapid generation of diverse complex molecules in environmentally benign manner. As mentioned, when one biodynamic heterocyclic system is coupled with another, a molecule with enhanced biological activity can be produced. Keeping in view the high potential of pyrroloindoles and pyrazoles as drug candidates, the synthesis of angularly fused pyrazolopyrroloindole derivatives was undertaken.

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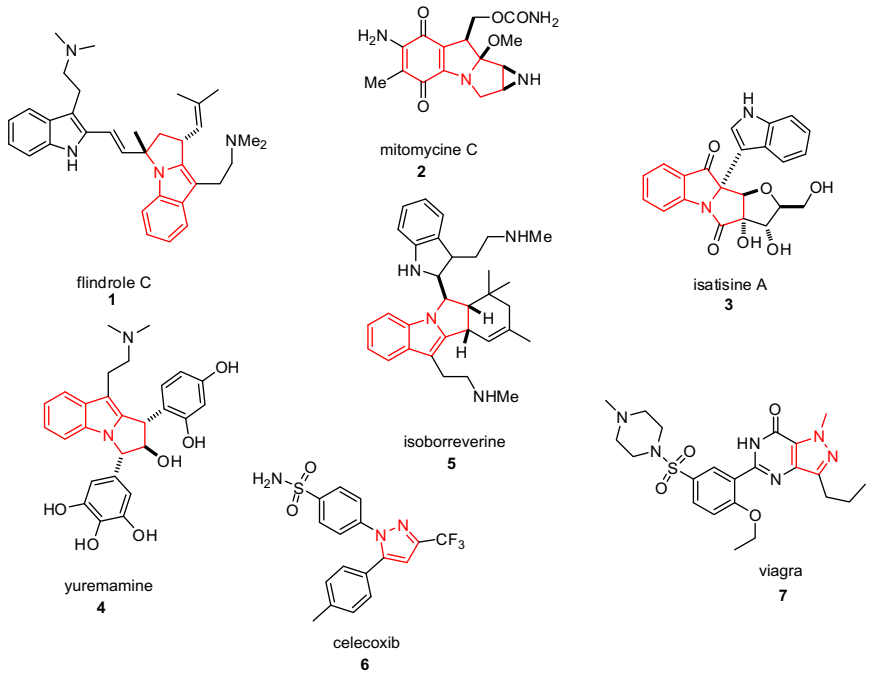
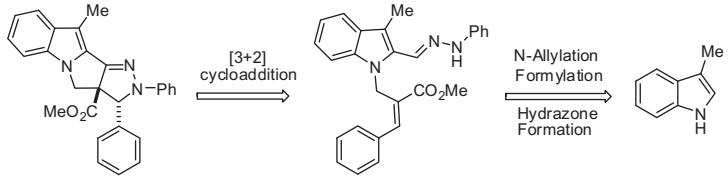
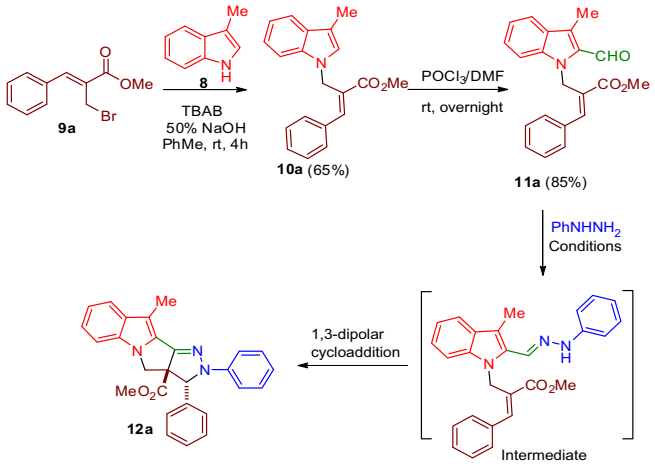


Figure 1. Representative examples of biologically active 1*H*-pyrrolo-[1,2-*a*]indole-based natural products and pyrazole-based drug molecules.



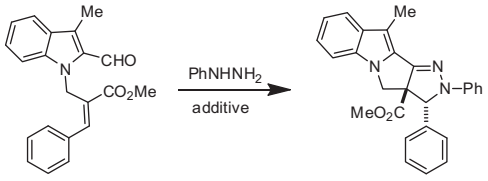
Scheme 1. Retrosynthetic strategy for the synthesis of [*a*]-annelated pyrazolopyrroloindoles.



Scheme 2. Synthesis of [*a*]-annelated pyrazolopyrroloindole.

Despite the importance of pyrroloindoles and pyrazoles, there are no reports for the synthesis of pyrazolopyrroloindoles via azomethine imine cycloaddition. Earlier, the synthesis of pyrazolopyrroloindoles was reported through nitrile imine cycloaddition but suffers from drawbacks like, use of the quantitative toxic metal reagent, lead tetraacetate for generation of nitrile imine dipole, tedious procedure and limited substrate scope.[22] Herein, we wish to report mild, metal-free synthesis of **[***a***]**-annelated pyrazolopyrroloindoles containing ring junction quaternary center via azomethine imine cycloaddition with simplified reaction

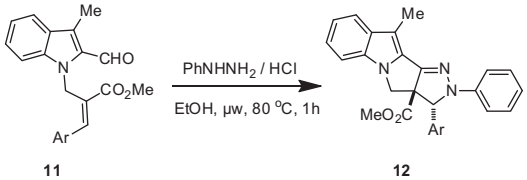
Table 1
Optimization of the reaction conditions for the synthesis of pyrazolopyrroloindole **12a**[a]



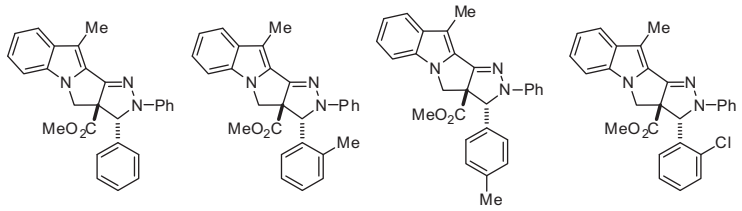
Entry	Solvent[b]/additive[c]	Condition	% Yield[d]
1	AcOH/H_2O (1:3)	100 °C, 24 h	40
2	AcOH/H_2O (1:3)	μw, 100 °C, 1 h	42
3[e]	AcOH/H_2O (1:3), NaOAc (0.3)	100 °C, 24 h	38
4[e]	AcOH/H_2O (1:3), NaOAc (0.3)	μw , 100 °C, 1 h	43
5[e]	AcOH/H_2O (1:3), NaOAc (0.3)	))), 38 °C, 2 h	28
6	AcOH/H_2O (1:3), PPh_3 (1)	100 °C, 18 h	40
7	DCM, $BF_3.(OEt)_3$	0 °C, 3 h	nr
8	Toluene, I_2 (2), DBU (2)	60 °C, 24 h	0
9	EtOH, HCl (5)[f]	80 °C, 24 h	25
10	EtOH, HCl (10)[f]	80 °C, 24 h	45
11	EtOH, HCl (15)[f]	80 °C, 24 h	35
12[g]	**EtOH, HCl (10)**[f]	**μw, 80 °C, 1 h**	**52**
13	MeOH, HCl (10)[f]	μw , 65 °C, 1 h	40
14	*n*-BuOH, HCl (10)[f]	μw , 120 °C, 1 h	Complex mixture

[a] Reaction conditions: **11a** (0.2 mmol), $PhNHNH_2$ (0.2 mmol), additive and 2 mL of solvent.
[b] Solvents ratio.
[c] Equivalents of additive.
[d] Isolated yield after column chromatography.
[e] Instead of $PhNHNH_2$, $PhNHNH_2$·HCl has been used.
[f] Concd HCl (37%) has been used.
[g] Optimized condition.

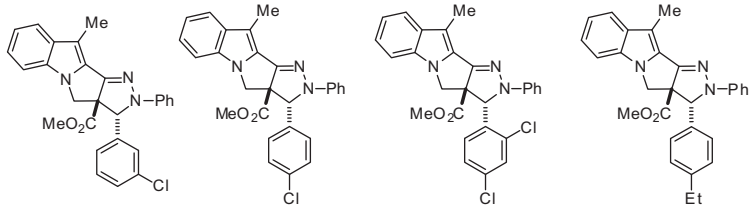
Table 2
Synthesis of variety of [*a*]-annelated pyrazolopyrrolo indoles **12**[a,b]



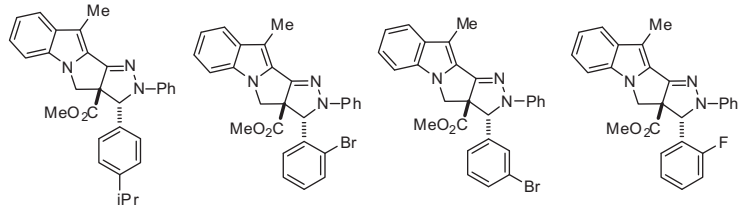
11 **12**



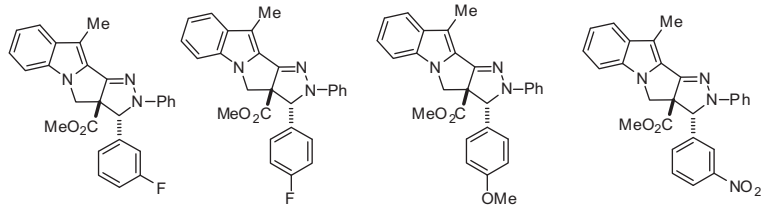
12a (52%) **12b** (55%) **12c** (51%) **12d** (43%)



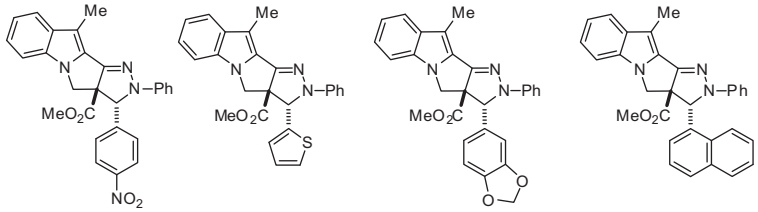
12e (45%) **12f** (37%) **12g** (40%) **12h** (56%)



12i (44%) **12j** (54%) **12k** (50%) **12l** (37%)



12m (50%) **12n** (42%) **12o** (43%) **12p** (-[c])

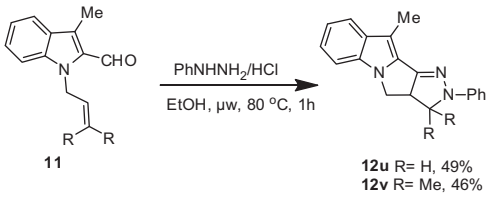


12q (-[c]) **12r** (50%) **12s** (43%) **12t** (40%)

[a] Reaction conditions: **11** (0.2 mmol), phenylhydrazine (0.2 mmol), concd HCl (37%) (2 mmol), EtOH (2 mL).
[b] Isolated yields after column chromatography.
[c] Complex reaction mixture formed.

procedure. Initially we envisaged that, Baylis–Hillman bromide based *N*-allylated indole-2-carboxaldehyde can be exploited in order to access the aforementioned tetracyclic framework through in situ formation of azomethine imine ylide followed by an intramolecular 1,3-dipolar cycloaddition reaction according to the retrosynthetic strategy shown in Scheme 1.

To manifest this, we started with (*Z*)-methyl 2-(bromomethyl)-3-phenylacrylate **9a** and reacted with 3-methylindole **8** to obtain *N*-allylated indole **10a** intermediate in good yield (65%). Further formylation of the *N*-allylated indole intermediate under Vilsmeier–Haack conditions led to corresponding aldehyde **11a** in excellent yield (85%) (Scheme 2). In order to optimize the reaction



Scheme 3. Synthesis of [*a*]-annelated pyrazolopyrroloindoles **12** from alkyl allyl systems **11**.

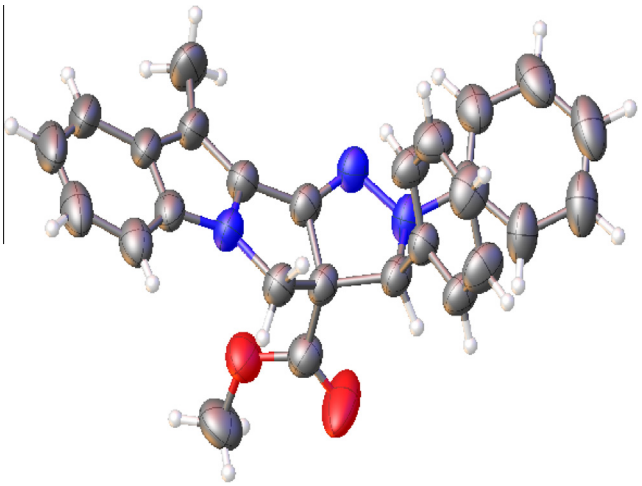


Figure 2. Crystal structure of compound **12a** (CCDC 976703).

conditions for the synthesis of pyrazolopyrroloindole **12a**, we choose (*E*)-methyl 2-((2-formyl-3-methyl-1*H*-indol-1-yl) methyl) -3-phenyl-acrylate **11a** as a model substrate and performed the reaction with phenylhydrazine (Table 1).

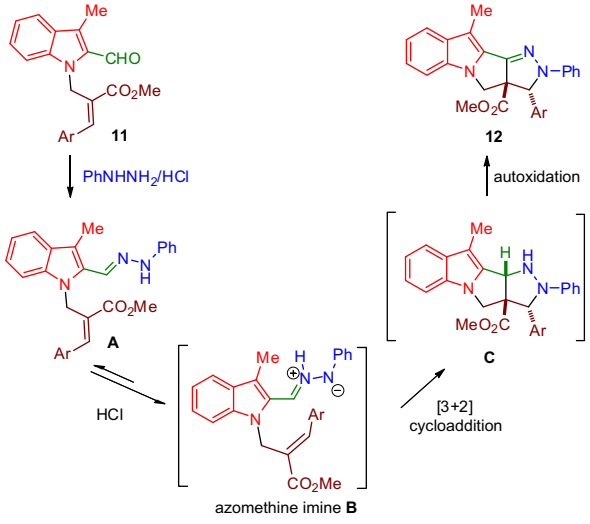
Initially, when we treated **11a** with $PhNHNH_2$/$PhNHNH_2$·HCl in the presence of AcOH/water (1:3) as a solvent system at various temperatures by conventional/microwave/ultrasound heating, it resulted in low to moderate yields of the desired product **12a** (Table 1, entries 1–6). A drastic reduction in the reaction time was observed under microwave irradiation (Table 1, entries 2 and 4). Utilization of Lewis acids like BF_3·$(OEt)_3$[23] and iodine,[24] which are known for the synthesis of pyrazole have failed to give the product (Table 1, entries 7 and 8). We have next examined, the reaction in the presence of HCl additive in various alcoholic solvents under conventional/microwave heating (Table 1, entries 9–14). Gratifyingly, the best result was obtained in the presence of 10 equiv of HCl in ethanol under microwave heating at 80 °C for 1 h to afford the desired product **12a** in 52% yield (Table 1, entry 12).

With the optimized reaction condition in hand, next we synthesized a series of substituted *N*-allylated indole-2-carboxaldehydes to explore the generality of the reaction. We have successfully extended the methodology to afford a variety of pyrazole-fused pyrroloindole derivatives in moderate to good yields, as shown in Table 2. It shows that the protocol is applicable to a wide range of aryl allylic systems with strong donating as well as withdrawing nature, except in the case of nitro-substituted allylic systems (**12p** and **12q**), which resulted in complex reaction mixtures (Table 2). The present protocol is also applicable for alkyl substituted allylic systems which afforded the products **12u** and **12v** in good yields (Scheme 3).

The structure and regiochemistry of the cycloadducts were confirmed by spectral analysis. Although, the NMR spectroscopic data support the formation of pyrazolopyrroloindoles **12**, the structure was unambiguously secured by an X-ray crystal structure analysis of compound **12a** (Fig. 2) (see SI for X-ray data of **12a**).

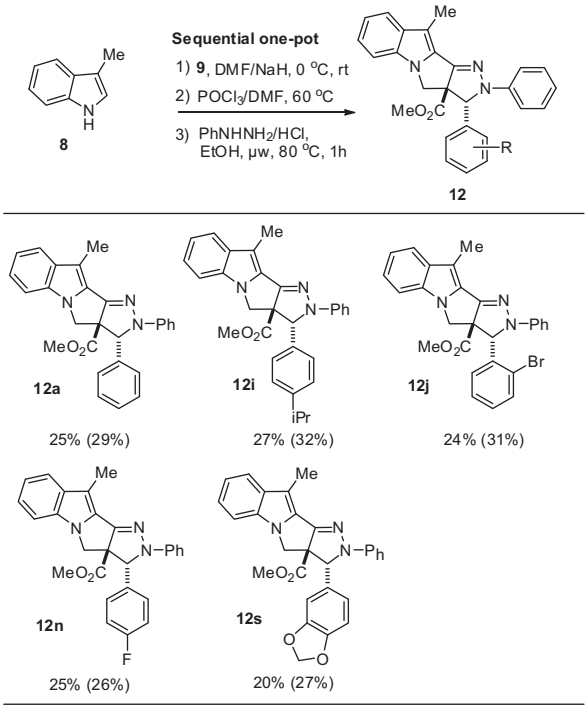
Mechanistically, the formation of **12** can be rationalized by the initial formation of hydrazone intermediate **A** by reaction of phenylhydrazine with aldehyde **11** which can be facilitated under acid catalysis.[25] Then intramolecular 1,3-dipolar cycloaddition of azomethine imine **B**[20,26] (formed in situ in presence of HCl) yields tetracyclic pyrazolidine **C**, which is spontaneously oxidized to pyrazolopyrroloindole **12**[27] (Scheme 4).

After having successfully developed the methodology, we were keen to examine the feasibility of a sequential one-pot protocol for



Scheme 4. Plausible reaction mechanism for the synthesis of pyrazolo-pyrroloindole **12** from aldehyde **11**.

Table 3
One-pot synthesis of [*a*]-annelated pyrazolopyrrolo-indoles **12**a,b



[a] Isolated yields after column chromatography.
[b] Numbers in parentheses refer to overall yields of the stepwise reactions (**8** → **10** → **11** → **12**).

the conversion of 3-methylindole **8** into pyrazolopyrroloindole **12a**. To our delight, this one-pot sequence has resulted in desired product with comparable yield. Even though our efforts to increase the yield failed, we have successfully synthesized pyrazolopyrroloindoles **12a**, **12i**, **12j**, **12n**, and **12s** (Table 3).

We have successfully developed a metal-free, facile intramolecular azomethine imine cycloaddition strategy for the synthesis of tetracyclic angularly fused [*a*]-annelated pyrazolopyrroloindoles containing an all carbon quaternary center at the ring fusion by using microwave irradiation. The important features of this protocol are rapid access to biologically relevant complex heterocyclic scaffolds, wide substrate scope, and good yields. In addition, a sequential one-pot synthesis of pyrazolopyrroloindole scaffolds featuring concurrent construction of two rings with two C–C, three C–N bond formations in good yields by avoiding tedious work-up and isolation of intermediates has been developed. Further, studies on biological activity of these fused tetracyclic compounds are currently under way.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.134.

References and notes

1. (a) Kodihalli, C. R.; Hosadu, M. V.; Vaidya, V. P. *ARKIVOC* **2008**, *xi*, 1; (b) Kumaraswamy, M. N.; Chandrashekhar, C.; Shivakumar, H.; Prathima Mathias, D. A.; Mahadevan, K. M.; Vaidya, V. P. *Indian J. Pharm. Sci.* **2008**, *70*, 715.
2. For a seminal review on pyrrolo[1,2-*a*]indoles, see: Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199.
3. For recent syntheses of pyrrolo[1,2-*a*]indoles, see: (a) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820; (b) Li, L.; Du, D.; Ren, J.; Wang, Z. *Eur. J. Org. Chem.* **2011**, 614; (c) Pyeon, H.-Y.; Pyo, S.-H.; Ahn, J.-K.; Kim, G.-C. *Bull. Korean Chem. Soc.* **2011**, 735; (d) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028; (e) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626; (f) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119; (g) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737.
4. (a) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864; (b) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329.
5. Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.
6. Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.
7. Vepsalainen, J. J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. C. *Planta Med.* **2005**, *71*, 1053.
8. (a)*1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484; (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765; (d) Kong, Y.; Tang, M.; Wang, Y. *Org. Lett.* **2014**, *16*, 576; (e) Lopchuk, J. M.; Hughes, R. P.; Gribble, G. W. *Org. Lett.* **2013**, *15*, 5218; (f) Korotaev, V. Y.; Barkov, A. Y.; Moshkin, V. S.; Matochkina, E. G.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron* **2013**, *69*, 8602; (g) Takaya, J.; Miyashita, Y.; Kusama, H.; Iwasawa, N. *Tetrahedron* **2011**, *67*, 4455; (h) Pospíšil, J.; Potáček, M. *Tetrahedron* **2007**, *63*, 337.
9. (a) Xu, L.-L.; Zheng, C.-J.; Sun, L.-P.; Miao, J.; Piao, H.-R. *Eur. J. Med. Chem.* **2012**, *48*, 174; (b) Vujasinovic, I.; Paravic-Radicevic, A.; Mlinaric-Majerski, K.; Brajsa, K.; Bertosa, B. *Bioorg. Med. Chem.* **2012**, *20*, 2101.
10. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Iwai, N.; Hiyama, Y.; Suzuki, K.; Ito, H.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J. *J. Med. Chem.* **2004**, *47*, 3693.
11. Geronikaki, A.; Babaev, E.; Dearden, J.; Dehaen, W.; Filimonov, D.; Galaeva, I.; Krajneva, V.; Lagunin, A.; Macaev, F.; Molodavkin, G.; Poroikov, V.; Pogrebnoi, S.; Saloutin, V.; Stepanchikova, A.; Stingaci, E.; Tkach, N.; Vlad, L.; Voronina, T. *Bioorg. Med. Chem.* **2004**, *12*, 6559.
12. (a) Theodoridis, G. Modern Crop Protection Compounds In In Krämer, W., Schirmer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; vol. 1, p 153; (b) Shiga, Y.; Okada, I.; Ikeda, Y.; Takizawa, E.; Fukuchi, T. *J. Pestic. Sci.* **2003**, *28*, 313.
13. (a) Sviridova, L. A.; Golubeva, G. A.; Tavtorkin, A. N.; Kochetkov, K. A. *Amino Acids* **2012**, *43*, 1225.
14. (a) Lang, S. A. J.; Lin, Y. I. Comprehensive Heterocyclic Chemistry In In Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; vol. 6, (b) Kotera, K.; Takano, Y.; Matsuura, A.; Kitahonoki, K. *Tetrahedron* **1970**, *26*, 539.
15. (a) Mishra, S. K.; Majumdar, P.; Behera, R. K.; Behera, A. K. *Synth. Commun.* **2014**, *44*, 32; (b) Zhang, G.; Ni, H.; Chen, W.; Shao, J.; Liu, H.; Chen, B.; Yu, Y. *Org. Lett.* **2013**, *15*, 5967; (c) Arepally, S.; Nagarajan, R. *Synthesis* **2013**, *45*, 1235; (d) Kim, S. H.; Lim, J. W.; Yu, J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2013**, *34*, 2915; (e) Verma, D.; Mobin, S. M.; Namboothiri, I. N. N. *J. Org. Chem.* **2011**, *76*, 4764; (f) Martin, A. R.; Mohanan, K.; Toupet, L.; Vasseur, J. J.; Smietana, M. *Eur. J. Org. Chem.* **2011**, 3184; (g) Muruganantham, R.; Namboothiri, I. N. N. *J. Org. Chem.* **2010**, *75*, 2197; (h) Mohanan, K.; Martin, A. R.; Toupet, L.; Smietana, M.; Vasseur, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3196; (i) Xie, J.-W.; Wang, Z.; Yang, W.-J.; Kong, L.-C.; Xu, D.-C. *Org. Biomol. Chem.* **2009**, *7*, 4352; (j) Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125.
16. (a) Na, R.; Liu, H.; Li, Z.; Wang, B.; Liu, J.; Wang, M. A.; Wang, M.; Zhong, J.; Guo, H. *Tetrahedron* **2012**, *68*, 2349; (b) Maiti, D. K.; Chatterjee, N.; Pandit, P.; Hota, S. K. *Chem. Commun.* **2010**, 2022; (c) Deng, X.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2412; (d) Dawood, K. M.; Fuchigami, T. *J. Org. Chem.* **2005**, *70*, 7537; (e) Molteni, G.; Ponti, A. *Chem. Eur. J.* **2003**, *9*, 2770; (f) Liu, B.; Wang, M.; Huang, Z. *Tetrahedron Lett.* **1999**, *40*, 7399; (g) Valle, J. L.; Polo, C.; Torroba, T.; Marcaccini, S. *J. Heterocycl. Chem.* **1995**, *32*, 899.
17. (a) Nayak, M.; Rastogi, N.; Batra, S. *Tetrahedron* **2013**, *69*, 5029.
18. (a) Li, Y.; Meng, Y.; Mengand, X.; Li, Z. *Tetrahedron* **2011**, *67*, 4002; (b) Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 3091; (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
19. (a) Helene, D.; Guerrand, S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 7921; (b) Galeta, J.; Man, S.; Bouillon, J.-P.; Potacek, M. *Eur. J. Org. Chem.* **2011**, 392; (c) Ren, H.; Ye, S.; Liu, F.; Wu, J. *Tetrahedron* **2010**, *66*, 8242; (d) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, 5238; (e) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790.
20. (a) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642; (b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruokajacs, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076; (c) Kanemasa, S.; Tomoshige, N.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3944.
21. (a)*Microwaves in Organic Synthesis*; Loupy, A., Ed., 2nd ed.; Wiley-VCH: Weinheim, Germany, 2006; (b) Moseley, J. D.; Kappe, C. O. *Green Chem.* **2011**, *13*, 794; (c) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127.
22. Prajapati, D.; Gadhwal, S. *Tetrahedron* **2004**, *60*, 4909.
23. Zhu, Y.; Wen, S.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 3553.

24. Srivastava, M.; Rai, P.; Singh, J.; Singh, J. *J. New Chem.* **2014**, *38*, 302.
25. (a) Kool, E. T.; Park, D.-H.; Crisalli, P. *J. Am. Chem. Soc.* **2013**, *135*, 17663; (b) Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1773.
26. Heating intermediate **A** (prepared separately) in absence of HCl failed to give required product **12**. However, heating in presence of HCl, resulted in product **12** with good yield, suggesting the role of HCl in the formation of azomethine imine **B** from **A**.
27. For similar kind of autoxidation see: Sun, B.; Adachi, K.; Noguchi *Tetrahedron* **1996**, *52*, 901.