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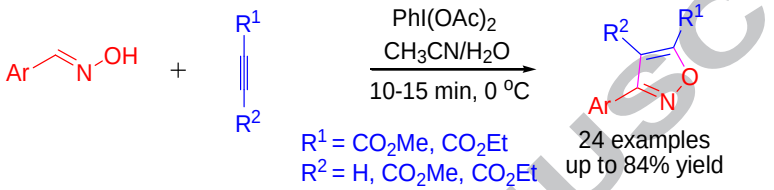

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# Hypervalent iodine mediated synthesis of di- and tri-substituted isoxazoles *via* [3+2] cycloaddition of nitrile oxides

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ABSTRACT

An efficient and rapid protocol for the synthesis of 3,4-disubstituted and 3,4,5-trisubstituted isoxazoles under catalyst-free conditions is described. This protocol involves pre-oxidation of aldoxime into nitrile oxide using diacetoxyiodobenzene. The *in situ* generated nitrile oxide was trapped with dipolarophiles for the formation of functionally rich isoxazoles *via* [3+2] cycloaddition.



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Nitrile oxides are key intermediates in the synthesis of many natural products.[1] These reactive species are highly unstable and readily undergo self-dimerization by dipolar cycloaddition in the absence of trapping agents to furnish furoxanes.[2,3] In presence of trapping reagents such as alkenes and alkynes these will undergo 1,3-dipolar cycloaddition leading to the formation of isoxazolines and isoxazoles.[4] Nitrile oxides are generally generated by the dehydrohalogenation of hydroxyiminoyl halides, dehydration of nitro compounds. An alternative oxidative hydrogenation of aldoximes was developed, and this method was applied for the synthesis of many of complex molecules.[5]

Isoxazole is a five-membered ring containing heterocyclic compound having *O*- and *N*-hetero atoms next to each other. Isoxazole motiff is ubiquitous in many natural products, biologically active molecules and chiral ligands.[6] Isoxazole derivatives display antibacterial, antiviral, anticancer, antiplatelet, analgesic, antinociceptive, anticonvulsant and immuno modulating activities.[7] These five-membered heterocycles are also potent towards COX-2 inhibitory, selective agonists at dopamine D4 receptors, exhibit GABA antagonist and also act as metabotropic glutamate receptor 1 antagonists.[8] Isoxazole unit is an integral part of natural products such as ibotenic acid, muscimol, isoxazole-4-carboxylic acid and drugs like valdecoxib, leflunomide, cloxacillin (Figure 1).[9] Numerous methods were reported for the past few decades for the synthesis of isoxazoles,[10] of which [3+2] dipolar cycloaddition of nitrile oxide and alkynes received much attention.[11] Fokin *et al.* developed Cu(I) and Ru(II) catalyzed 1,3-dipolar cycloaddition of nitrile oxides with terminal alkynes and this protocol was well

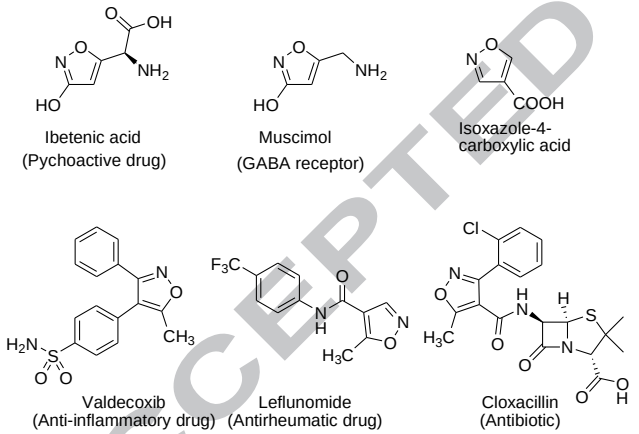


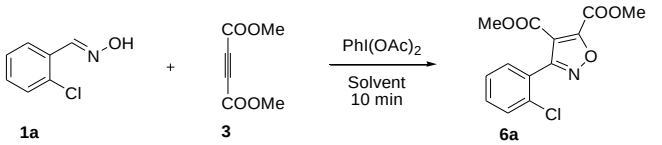

**Figure 1**. Some natural products and drugs containing isoxazole ring.

established to synthesize the regioselective 3,4-disubstituted and 3,5-disubstituted isoxazoles.[12] Most of the metal complexes are toxic in nature and because of this a metal-free protocol is still desirable in this area. Owing to their readily availability and easy handling, hypervalent iodine reagents are more suitable for the synthesis of isoxazoles. A plethora of chemical reactions were described in the literature for the synthesis of isoxazoles/ isoxazoline derivatives from the reaction of aldoxime with alkenes and alkynes in the presence of stoichiometric amount of hypervalent iodine reagents such as iodosylbenzene,[13] hydroxytosyloxyiodobenzene,[10p,14] dichloroiodobenzene,[15] diacetoxyiodobenzene ,[16] and bis(trifluoroacetoxy)iodobenzene.[17] Recently, Zhdankin *et al.* reported[18] hypervalent iodine catalyzed synthesis of isoxazole/isoxazoline derivatives using oxone as terminal oxidant. In all these reactions, initially the aldoxime gets converted into nitrile oxide which undergoes [3+2] cycloaddition with alkyne derivatives to afford the isoxazole derivatives.

Inspired by the protocols reported for the synthesis of isoxazoles and their applications, we were interested to develop a simple, mild and rapid protocol for the synthesis of 3,4-di- and 3,4,5-tri-substituted isoxazoles bearing electron-deficient groups from easily accessible starting materials. Accordingly, we designed a one-pot strategy for the synthesis of isoxazoles *via* [3+2] cycloaddition of *in situ* generated nitrile oxides with dipolarophiles.

In continuation of our research on hypervalent iodine mediated reactions,[19] herein, we report the diacetoxyiodobenzene (DIB)-mediated simple and rapid protocol for the synthesis of isoxazole derivatives from aldoximes *via* [3+2] dipolar cycloaddition of *in situ* generated nitrile oxides with alkynes bearing electron-deficient groups, respectively. Initially we focused on optimization of reaction conditions. For this, we have chosen 2-chlorobenzaldehyde oxime (**1a**) and dimethyl acetylenedicarboxylate (DMAD, **3**) as model reactants to arrive at the optimal condition. In a preliminary experiment, to a mixture of 2-chlorobenzaldehyde oxime (**1a**) and dimethyl acetylenedicarboxylate (**3**) in acetonitrile, was added a solution of 1.2 equiv of DIB in acetonitrile drop-wise over a period of 5 min at 0 $^{o}$C. The expected isoxazole derivative **6a** was obtained in 24% yield in 5 min (Table 1, entry 1). The structure of the product was confirmed upon carefull analysis of the data obtained from $^{1}$H and $^{13}$C NMR spectra. The product **6a** was obtained from the [3+2] dipolar cycloaddition of *in situ* generated nitrile oxide (**2a**) from the aldoxime **1a** in the presence of DIB with dimethyl acetylenedicarboxylate. In order to obtain the optimal condition, a detailed screening was adopted by varying solvents and temperature. The results are shown in Table 1. When we performed the reaction in methanol at 0 $^{o}$C, isoxazole **6a** was obtained in 68% yield (Table 1, entry 2). To further improve the yield of the product, we have performed the reaction in water and acetonitrile/water (2:1) (Table 1, entries 3–5). When we carried out the reaction in water at 0 $^{o}$C, the isoxazole **6a** was obtained in low yield (Table 1, entry 3). The same reaction was

**Table 1.** Optimization of reaction conditions[a]




| Entry | Solvent | Temperature | Yield (%)[b] |
|---|---|---|---|
| 1 | MeCN | 0 $^{o}$C | 24 |
| 2 | MeOH | 0 $^{o}$C | 68 |
| 3 | $H_2O$ | 0 $^{o}$C | 30 |
| 4 | MeCN/$H_2O$ (2:1) | rt | 42 |
| 5 | MeCN/$H_2O$ (2:1) | 0 $^{o}$C | 84 |

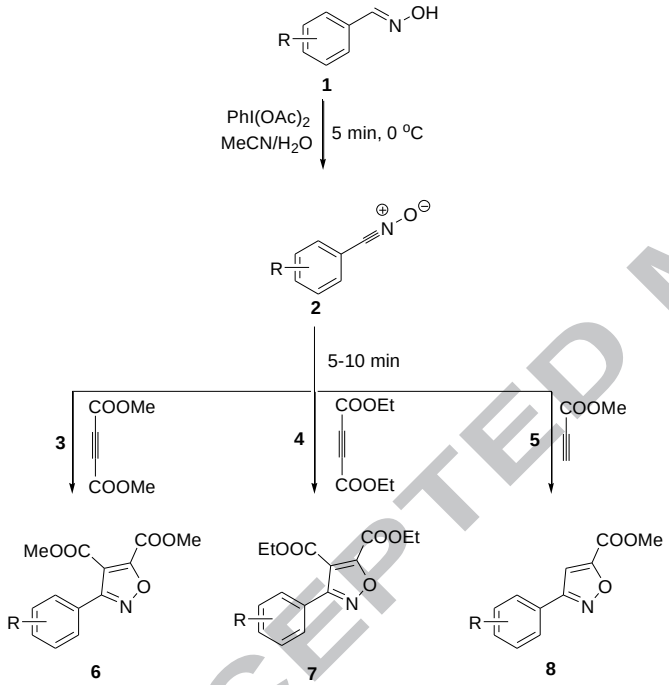
[a] Reactions were performed with 2-chlorobenzaldehyde oxime (**1a**, 1 mmol) and dimethyl acetylenedicarboxylate (**3**, 1.5 mmol) in the presence of diacetoxyiodobenzene (1.2 mmol).

[b] Pure and isolated yield.

performed in a 2:1 mixture of acetonitrile/water at rt and the isoxazole **6a** was isolated in acceptable yield (Table 1, entry 4). A remarkable increment in the yield of isoxazole derivative **6a** was noticed, when the reaction was performed in acetonitrile/water (2:1) mixture at 0 $^{o}$C (Table 1, entry 5).

Having optimized conditions in hand to determine the scope and generality of the present protocol, various aldoximes having different substitutions on arene moiety were probed. For this, we

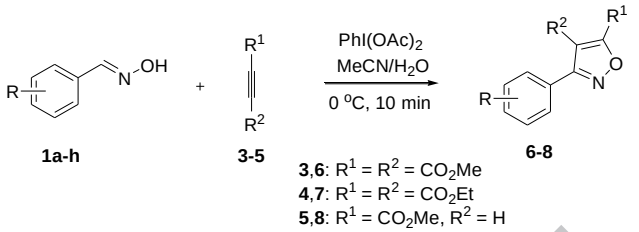
have chosen a series of benzaldehyde oximes **1a-h** and different dipolarophiles such as DMAD (**3**) and diethyl acetylenedicarboxylate (DEAD, **4**). Under the standard conditions the nitrile oxides, generated from aldoximes in presence of DIB, undergone [3+2] dipolar cycloaddition with dipolarophiles **3** and **4** smoothly to afford the corresponding isoxazoles. The reactions, carried out with various benzaldehyde oximes **1a-h** and DMAD, were completed in 10 min to obtain the isoxazole derivatives **6a-h** in 41–82% yield. Similarly, the reactions of **1a-h** with **DEAD** proceeded rapidly to afford the corresponding isoxazoles **7a-h** in 52–67% yield (Table 2, Scheme 1). After successfully carrying out the reactions of benzaldehyde oximes with DMAD and DEAD, we have further explored the scope of the present protocol by selecting methyl propiolate (**5**) as dipolarophile. The [3+2] dipolar cycloaddition of nitrile oxides, derived from benzaldehyde oximes **1a-e**, with methyl propiolate resulted in the formation of isoxazole derivatives **8a-e** in good yield in the range of 62–67% (Scheme 1, Table 2).




**Scheme 1.** [3+2] Dipolar cycloaddition of *in situ* generated nitrile oxides **2a-h** with dipolarophiles **3-5**.

We have further extended our strategy for [3+2] dipolar cycloaddition of nitrile oxide **2i** derived from 1-naphthaldehyde oxime (**1i**) with dipolarophiles **3-5**. The reactions of 1-naphthaldehyde oxime with dipolarophiles, under optimized conditions, provided the corresponding isoxazole derivatives **6i–8i** in 63–83% yield (Scheme 2). The given regiochemistry in structures of **8a-e** are based on the $^{1}$H NMR data reported for **8d** and similar isoxazoles.[10k,10n,10p,10r]

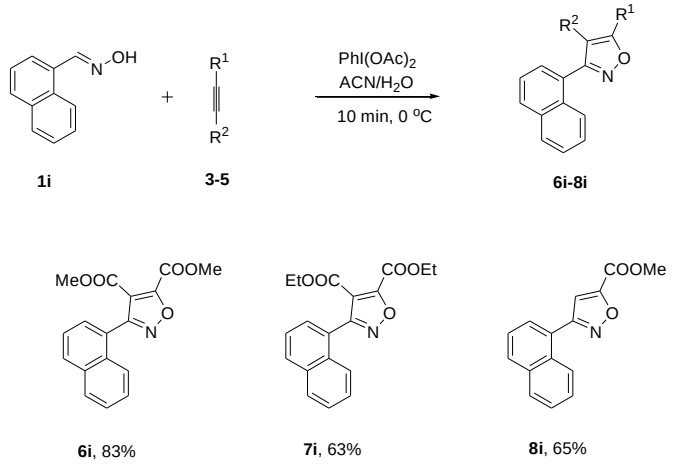
**Table 2.** Substrate scope[a]



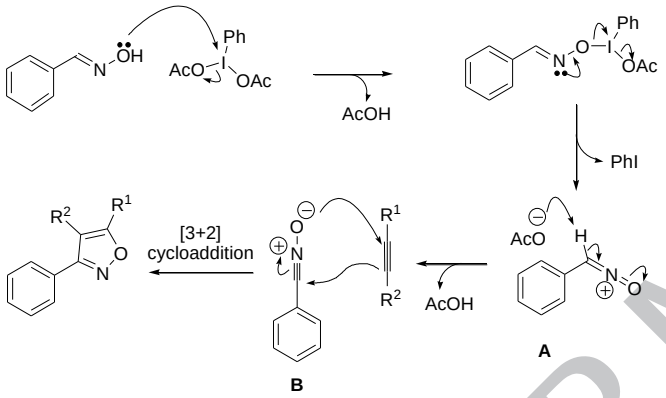

| Entry | Aldoxime | | Dipolarophile | Product | Yield (%)[b] |
|---|---|---|---|---|---|
| | **1** | R | | | |
| 1 | **1a** | 2-Cl | **3** | **6a** | 84 |
| 2 | **1a** | 2-Cl | **4** | **7a** | 58 |
| 3 | **1a** | 2-Cl | **5** | **8a** | 52 |
| 4 | **1b** | 3-OMe, 4-OMe | **3** | **6b** | 57 |
| 5 | **1b** | 3-OMe, 4-OMe | **4** | **7b** | 52 |
| 6 | **1b** | 3-OMe, 4-OMe | **5** | **8b** | 62 |
| 7 | **1c** | 4-Me | **3** | **6c** | 60 |
| 8 | **1c** | 4-Me | **4** | **7c** | 80 |
| 9 | **1c** | 4-Me | **5** | **8c** | 65 |
| 10 | **1d** | H | **3** | **6d** | 57 |
| 11 | **1d** | H | **4** | **7d** | 40 |
| 12 | **1d** | H | **5** | **8d** | 77 |
| 13 | **1e** | 2-OMe | **3** | **6e** | 54 |
| 14 | **1e** | 2-OMe | **4** | **7e** | 52 |
| 15 | **1e** | 2-OMe | **5** | **8e** | 57 |
| 16 | **1f** | 4-Cl | **3** | **6f** | 52 |
| 17 | **1f** | 4-Cl | **4** | **7f** | 58 |
| 18 | **1g** | 4-OMe | **3** | **6g** | 64 |
| 19 | **1g** | 4-OMe | **4** | **7g** | 71 |
| 20 | **1h** | 3-$NO_2$ | **3** | **6h** | 41 |
| 21 | **1h** | 3-$NO_2$ | **4** | **7h** | 64 |

[a] Reactions were performed with oxime **1** (1 mmol) and dipolarophile (**3**/**4**/**5**, 1.5 mmol) in the presence of diacetoxyiodobenzene (1.2 mmol). [b] Pure and isolated yield.

A plausible mechanism for the formation of isoxazole derivatives is depicted in Scheme 3. Initially, the nucleophilic oxygen atom of the benzaldehyde oxime attacks the electrophilic iodine centre leading to the release of one of the acetate ions from DIB. The influence of the nucleofugality of the phenyliodanyl group helps the two-electron reduction of the iodine(III) center with concomitant elimination of a monovalent iodide and a second acetate ion to generate the intermediate **A**. The acetate ion from the previous step, abstracts proton from benzylic position leading to the formation of nitrile oxide intermediate **B**. The *in situ* generated nitrile oxide undergoes [3+2] dipolar cycloaddition with alkyne derivative to afford the corresponding isoxazole derivative.




**Scheme 2.** DIB-Mediated reaction of 1-naphthaldehyde oxime **1i** with dipolarophiles **3**–**5**.




**Scheme 3**. Plausible mechanism for the formation of isoxazole derivatives.

In summary, we have developed a rapid, simple and efficient protocol for the synthesis of isoxazole derivative from easily available starting materials under catalyst-free and mild reaction conditions. The simplicity of experimental procedure and readily availability of starting materials render this strategy as an attractive method for the synthesis of isoxazole derivatives bearing electron-deficient functionalities.

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## References and notes

1. (a) Grundmann. C. *Synthesis* **1970**, 344; (b) Grundmann. C; Grunanger. P. The 'Nitrile oxides', Springer-verlag. Berlin and New York. **1971**; (c) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736; (d) Paek, S.-M.; Suh, Y.-G. *Molecules* **2011**, *16*, 4850.
2. Beltrame, P.; Comotti, A.; Vegleo, C. *Chem. Commun.* **1967**, *19*, 996.
3. Dondoni , A.; Mangini, A.; Ghersetti, S. *Tetrahedron Lett.* **1966**, *7*, 4789.
4. (a) Padwa, A. 1,3-Dipolar Cycloaddition Chemistry; Ed.; Wiley: New York, **1984**; Vols. 1; (b) Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985; (c) Torssell, K. B. G. Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis; VCH: New York, **1988**; (d) Chen, W.; Zhang, J.; Wang, B.; Zhao, Z.; Wang, X.; Hu, Y. *J. Org. Chem.* **2015**, *80*, 2413; (e) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. *RSC Adv.* **2015**, *5*, 3470.
5. Dong, K.-Y.; Qin, H.-T.; Bao, X.-X.; Liu, F.; Zhu, C. *Org. Lett.* **2014**, *16*, 5266.
6. (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410; (b) Jaeger, V.; Colinas, P. A. Nitrile Oxide. In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Padwa, A., Pearson, W. H., Eds.; Chemistry of Heterocyclic Compounds; Wiley: Hoboken, N. J. **2002**; Vol. 59, p 361; (c) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247; (d) Tapadar, S.; He, R.; Luchini, D. N.; Billadeau, D. D.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3023; (e) Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V. Handbook of Heterocyclic Chemistry, 3rd Ed.; Elsevier: Oxford, **2010**; (f) Takenaka, K.; Nagano, T.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 379.
7. (a) Tomita, K.; Takahi, Y.; Ishizuka, R.; Kamamura, S.; Nakagawa, M.; Ando, M.; Nakanishi, T.; Nakamura, T.; Udaira, H. *Ann. Sankyo Res. Lab.* **1973**, *1*, 25; *Chem. Abstr.* **1974**, *80*, 120808; (b) Daidone, G.; Raffa, D.; Maggio, B.; Plescia, F.; Cutuli, V. M. C.; Mangano, N. G.; Caruso, A. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 50; (c) Giovannoni, M. P.; Vergelli, C.; Ghelardini, C.; Galeotti, N.; Bartolini, A.; Piaz, V. K. *J. Med. Chem.* **2003**, *46*, 1055; (d) Li, W.-T.; Hwang, D.-R.; Chen, C.-P.; Shen, C.-W.; Huang, C.-L.; Chen, T.-W.; Lin, C.-H.; Chang, Y.-L.; Chang, Y.-Y.; Lo, Y.-K.; Tseng, H.-Y.; Lin, C.-C.; Song, J.-S.; Chen, H.-C.; Chen, S.-J.; Wu, S.-H.; Chen, C.-T. *J. Med. Chem.* **2003**, *46*, 1706; (e) Gutierrez, M.; Amigo, J.; Fuentes, E.; Palomo, I.; Astudillo, L. Platelets **2014**, *25*, 234; (f)Yong, J.-P.; Lu, C.-Z.; Wu, X.; *Anti-Cancer Agents in Med. Chem.* **2015**, *15*, 131.
8. (a) Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Ragan, C. I. *J. Med. Chem.* **1996**, *39*, 1943; (b) Talley, J. J. *Prog. Med. Chem.* **1999**, *13*, 201; (c) Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775; (d) Frolund, B.; Jorgensen, A. T.; Tagmose, L.; Stensbol, T. B.; Vestergaard, H. T.; Engblom, C.; Kristiansen, U.; Sanchez, C.; KrogsgaardLarsen, P.; Liljefors, T. *J. Med. Chem.* **2002**, *45*, 2454; (e) Cho, G. H.; Kim, T.; Son, W. S.; Seo, S. H.; Min, S.-J.; Cho, Y. S.; Keum, G.; Jeong, K.-S.; Koh, H. Y.; Lee, J.; Pae, A. N. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1324.
9. (a) Kobinata, K.; Sekido, S.; Uramoto, M.; Ubukato, M.; Osada, H.; Yamaguchi, I.; Isono, K. *Agric. Biol. Chem.* **1991**, *55*, 1416; (b) Rozman, B.; Praprotnik, S.; Logar, D.; Tomsic, M.; Hijnik, M.; Kos-Golja, M.; Dolenc, P. *Ann. Rheum. Dis.* **2002**, *61*, 567; (c) Lawrence, S. L.; Roth, V.; Slinger, R.; Toye, B.; Gaboury, I.; Lemyre, B. *BMC Pediatrics* **2005**, *5*, 49; (d) Sperry, J.; Wright, D. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723; (e) Shin, K. D.; Lee, M.-Y.; Shin, D.-S.; Lee, S.; Son, K.-H.; Koh, S.; Paik, Y.-K.; Kwon, B.-M.; Han, D. C. *J. Biol. Chem.* **2005**, *50*, 41439; (f) Lee, Y.-S.; Park, S. M.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126.
10. (a) Franz J. E.; Pearl H. K. *J. Org. Chem.* **1976**, *41*, 1296; (b) Anderson, W. K.; Jones, A. N. *J. Med. Chem.* **1984**, *27*, 1559; (c) Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1985**, *17*, 3076; (d)Yokoyama, M.; Tsuji, K.; Kushida, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 67; (e) Zen, S.; Harada, K.; Nakamura, H.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2881; (f) Kumar, A.; Maruya, R. A.; Sharma, S.; Ahmad, P.; Singh, A. B.; Tamrakar, A. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2009**, *17*, 5285; (g) Wang, Y.-G.; Xu, W.-M.; Huang, X. *Synthesis* **2007**, 28; (h) Mazzei, M.; Balbi, A.; Sottofattori, E.; Garzoglio, R.; Montis, A. D.; Corrias, S.; Colla, P. L. *Eur. J. Med. Chem.* **1993**, *28*, 669; (i) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203; (j) Waldoand, J. P.; Larock, R. C. *Org. Lett.* **2007**, *72*, 9643; (k) Dadiboyena S.; Xu, J.; Hamme, A. T. *Tetrahedron Lett.* **2007**, *48*, 1295; (l) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *Org. Lett.* **2009**, *11*, 3982; (m) Praveen, C.; Kalyanasundaram, A.; Perumal, P. T. *Synlett* **2010**, 777; (n) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda Y. *Org. Lett.* **2011**, *13*, 2966. (o) Mo, D.-L.; Wink, D. A.; Anderson, L. L. *Org. Lett.* **2012**, *14*, 5180; (p) Jadhav, R. D.; Mistry, H. D.; Motiwala H.; Kadam, K. S, Kandre S.; Gupte A.; Gangopadhyay, A. K.; Sharma R. *J. Heterocyclic Chem.* **2013**, *50*, 774. (q) Zhang, L.; Zeng, Q.; Mao, A.; Wu, Z.; Luo, T.; Xiao, Y.; Zhang, J. *Org. Biomol. Chem.* **2014**, *12*, 8942; (r) Han, L.; Zhang, B.; Zhu, M.; Yan, J. *Tetrahedron Lett.* **2014**, *55*, 2308.
11. (a) Huisgen, R. 1,3-Dipolar Cycloaddition Chemistry, ed. Padwa, A. Wiley, New York, **1984**, vol. 1, p. 1; (b) Jaeger, V.; Colinas, P. A. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products, Padwa, A. Eds. Wiley, Hoboken, **2002**, vol. 59, p. 361; (c) Beha, S.; Giguere, D.; Patnam, R.; Roy, R.; *Synlett* **2006**, 1739; (d) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839; (e) Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043 and references therein.

12. (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovstev, V. V.; Noodleman, L.; Sharpless K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2004**, *127*, 210; (b) Hansen, T. V.; Peng W.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761; (c) Grecian S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285.
13. (a) Tanaka, S.; Ito, M.; Kishikawa, K.; Khmoto, S.; Yamamoto, M. *Nippon Kagaku Kaishi* **2002**, *3*, 471; (b) Chatterjee, N.; Pandit, P.; Halder, S.; Patra, A.; Maiti, D. K. *J. Org. Chem.* **2008**, *73*, 7775.
14. (a) De, S. K.; Mallik, A. K. *Tetrahedron Lett.* **1998**, *39*, 2389; (b) Raihan, M. J.; Kavala, V.; Kuo, C.-W.; Raju, R.; Yao, C.-F. *Green Chem.* **2010**, *12*, 1090.
15. Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 1625.
16. (a) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Reddy, M. R.; *Tetrahedron Lett.* **2004**, *45*, 7347; (b) Das, B.; Holla, H.; Mahender, G.; Venkateswarlu, K.; Bandgar, B. P.; *Synthesis* **2005**, 1572; (c) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539; (d) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394; (e) Turner, C. D.; Ciufolini, M. A. *ARKIVOC* **2011**, (*i*), 410; (f) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728.
17. (a) Jawalekar, A. M.; Reubsaet, E.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Commun.* **2011**, 47, 3198; (b) Niu, T.-F.; Lv, M.-f.; Wang, L.; Yi, W.-b.; Cai, C. *Org. Biomol. Chem.* **2013**, *11*, 1040.
18. Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010.
19. (a) Surasani, S. R.; Rajora, V. S.; Bodipati, N.; Peddinti, R. K. *Tetrahedron Lett.* **2009**, *50*, 773; (b) Surasani, S. R.; R. K. *Tetrahedron Lett.* **2011**, *52*, 4615; (c) Bodipati, N.; Peddinti, R. K. *Org. Biomol. Chem.* **2012**, *10*, 1958; (d) Bodipati, N.; Peddinti, R. K. *Org. Biomol. Chem.* **2012**, *10*, 4549; (e) Parumala, S. K. R.; Peddinti, R. K. *Org. Lett.* **2013**, *15*, 3546; (f) Parumala, S. K. R.; Surasani, S. R.; Peddinti, R. K. *New J. Chem.* **2014**, *38*, 5268; (g) Surasani, S. R.; Parumala, S. K. R.; Peddinti, R. K. *Org. Biomol. Chem.* **2014**, *12*, 5656; (h) Naganaboina, R. T.; Peddinti, R. K. *Tetrahedron* **2015**, *71*, 6245.
20. *General procedure for the synthesis of various substituted isoxazole derivatives:* A mixture of benzaldehyde oxime derivative **1** (0.5 mmol, 1 equiv) and 1.5 equiv of dialkyl acetylenedicarboxylate (**3** or **4**) or methyl propiolate (**5**), dissolved in 6 mL of a 2:1 acetonitrile/water mixture. To this diacetoxyiodobenzene (DIB) (0.60 mmol, 1.2 equiv) solution in 4 mL water was added drop-wise over a period of 5 min at 0 $^{o}$C. After complete addition of DIB, the reaction was monitored by TLC at regular time intervals. After completion of the reaction (additional 5–10 min), the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate and washed with water and extracted thrice (3 x 10 mL) with ethyl acetate. The organic layer was dried over anhyd. $Na_2SO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography using 5–10% ethyl acetate in hexanes as eluent to obtain pure isoxazole compound.
21. *Characterization data for selected compounds:*

**Dimethyl 3-(2-chlorophenyl)isoxazole-4,5-dicarboxylate (6a):**
Reaction time: 10 min; Yield: 123 mg (84%) as yellow viscous liquid; IR (KBr): $\nu_{max}$ 3066, 2957, 2854, 1736, 1603, 1444, 1315, 1079, 812, 653 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.51–7.43 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 4.04 (s, 3H), 3.77 (s, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 160.9, 160.3, 160.2, 156.7, 133.5, 131.5, 131.3, 129.7, 126.9, 126.6, 116.1, 53.4, 52.7 ppm; HRMS (ESI+) *m/z* calcd for $C_{13}H_{10}ClNO_5Na$ [M + Na]$^{+}$: 318.0140, found 318.0139.

**Diethyl 3-(3,4-dimethoxyphenyl)isoxazole-4,5-dicarboxylate (7b):**
Reaction time: 10 min; Yield: 91 mg (52%) as yellow viscous liquid; IR (KBr): $\nu_{max}$ 2984, 2843, 1715, 1598, 1465, 1286, 1150, 1077, 865, 767, 720 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.90 (s, 6H), 1.40 (t, *J* = 7.0 Hz, 3H) 1.32 (t, *J* = 7.0 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 161.7, 160.7, 159.2, 156.1, 151.0, 149.1, 121.1, 119.4, 116.1, 111.0, 110.9, 62.8, 62.4, 56.0, 55.9, 13.9, 13.8 ppm; HRMS (ESI+) *m/z* calcd for $C_{17}H_{19}NO_7Na$ [M + Na]$^{+}$: 372.1054, found 372.1055.

**Methyl 3-(*p*-tolyl)isoxazole-5-carboxylate (8c):**
Reaction time: 10 min; Yield: 71 mg (65%) as white solid; MP: 98 $^{o}$C; IR (KBr): $\nu_{max}$ 3125, 2952, 2849, 1724, 1612, 1456, 1288, 1127, 1003, 912, 817, 676 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.29 (s, 1H), 4.02 (s, 3H), 2.44 (s, 3H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 157.0, 155.9, 154.4, 154.2, 153.4, 133.8, 122.7, 119.7, 118.0, 100.4, 45.8, 14.4 ppm; HRMS (ESI+) *m/z* calcd for $C_{12}H_{11}NO_3Na$ [M + Na]$^{+}$: 240.0631, found 240.0616.