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A new simple and efficient metal-free 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promoted regioselective synthesis of 3,5-disubstituted isoxazoles and isoxazolines from aldoximes has been described. This method allows reaction to proceed efficiently on aldoximes containing unprotected phenolic hydroxyl group. Furthermore, with the use of higher equivalents of N-chlorosuccinimide, chloro-substituted isoxazoles and isoxazolines were obtained as the only products via tandem one-pot 1,3-dipolar cycloaddition followed by regioselective chlorination.

Isoxazoles and isoxazolines are five-membered nitrogen containing heterocycles commonly found in variety of natural products and drugs and are known to exhibit wide range of pharmacological activities. The structures of biologically active isoxazoles/ isoxazolines A–E are shown in Figure 1.  

**Figure 1.** Examples of bioactive isoxazoles and isoxazolines

Although numerous methods have been reported for synthesis of isoxazoles, the cycloaddition of alkyne with nitrile oxides is probably the most direct route to access these heterocycles. Uncatalyzed thermal cycloaddition reaction of nitrile oxide with alkyne is neither chemos- nor regioselective and, as a consequence, leads to formation of multiple products. Mostly the regioselectivity in this reaction has been achieved using Cu catalysts. There also exists few metal-free protocols for synthesis of isoxazoles; however most of these reports involve use of hypervalent iodine. Many hypervalent iodine reagents are explosive and have chemical reactivity issues. Apart from the use of hypervalent iodine, only two other metal-free conditions (Et₃N, NaOCl/Et₃N) have been reported. However, the former reaction was not suitable for phenolic hydroxyl containing aldoximes; and later condition has been reported for only one example. The detailed substrate scope has never been established. In this context, we thought of exploiting this reaction to establish an efficient and elegant metal-free protocol for synthesis of isoxazoles and isoxazolines with broad substrate scope. Our efforts identified 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an excellent reagent which promotes 1,3-dipolar addition of nitrile oxides with alkenes without need of any metal catalyst. DBU has been reported to promote synthesis of variety of heterocyclic scaffolds such as isquinolinones and benzothiazoles. Herein, we report DBU-promoted synthesis of 3,5-disubstituted isoxazoles. Furthermore, we also report an interesting DBU-promoted tandem one-pot 1,3-dipolar cycloaddition reaction followed by regioselective chlorination (Figure 2).

**Figure 2.** DBU promoted synthesis of isoxazoles and isoxazolines

Our investigations were started with the reaction of chloroaldoxime 2a with phenylacetylene 3a in presence of 1 equiv DBU in chloroform, which produced desired 3,5-disubstituted isoxazole 4a in 10 min in 95% yield (Figure 3). Next, we elaborated this method for direct synthesis of isoxazole 4a from aldoxime 1a. Under similar reaction conditions, when the reaction of 4-hydroxyphenyl aldoxime 2a with phenylacetylene 3a in presence of 1.2 equiv NCS was performed, multiple products were formed. Further, optimization studies indicated that DMF is the best solvent for this reaction and sequential addition is required to get desired product in good yield (Figure 3). The sequential addition (1a+ NCS+DMF, rt, 1 h followed by addition of DBU and 3a, rt, 10 min) was followed, to get product 4a in good yield, without formation of side-products. However, when we performed this reaction (from 1a) in presence of Et₃N (in place of DBU) under similar reaction conditions, multiple...
products were formed; which clearly indicated the superiority of our protocol over earlier Et$_2$N$^+$ method. The addition of DBU is slightly exothermic and quickly converts aldoximes to nitrite oxides which subsequently reacts with respective alkynes/alkenes to produce desired heterocycles. It is noteworthy to mention that the direct synthesis of hydroxy-substituted phenyl isoxazole 4a from corresponding nitrite oxide has never been reported. The limitation of earlier methods for hydroxy-substituted phenyl nitrite oxides has also been mentioned. However, the present DBU-promoted synthesis provided this product in excellent yield.

Figure 3. DBU-promoted synthesis of 4-hydroxy substituted isoxazole 4a. Reagents and conditions: (a) 1 equiv DBU, CHCl$_3$, rt, 10 min, 95%; (b) 1 equiv DBU, 1.2 equiv NCS, DMF, 1 h, 80%.

Next, the substrate scope of the reaction was investigated for variety of aldoximes and phenylacetylenes (Figure 4). The optimized reaction condition involving the use of 1 equiv of DBU and 1.2 equiv of NCS was employed. Phenyl aldoxime along with those substituted with alkyl electron-donating groups produced isoxazoles in excellent yields (examples 4b, 4d, 4e, and 4i). In case of aldoximes substituted with other electron-donating groups such as OH, OMe (examples 4a, 4c, 4f, 4g and 4j), desired products were formed in 65-80% yield. Interestingly, in latter reactions, additionally a ring-chlorinated isoxazole products were obtained as side products in 10-20% yield. Heterocyclic aldoximes also participated well in this reaction, producing desired products 4k and 4l in good yields. It is noteworthy to mention that the pyridine linked isoxazole 4l prepared herein, has a close structural similarity to that of nicotine receptor modulator (structure D, Figure 1). Aliphatic oximes (example 4m) and phenyl aldoxime with electron-withdrawing group (example 4n) does not participated in this reaction. Among alkynes, all substituted phenylacetylenes participated well in this reaction, whereas aliphatic alkynes such as propargyl alcohol (example 4j) and N-propargylated isatin (example 4h) produced lower yields.

Figure 4. Scope of the reaction for synthesis of isoxazoles. Reagents and conditions: aldoxime (1 equiv.), alkyn (1.2 equiv.), DBU (1 equiv.), NCS (1.2 equiv.), DMF, 1-8 h, 50-88%. Reaction time: 1 h for 4a, 4f, 4g and 4j; and 8 h for other examples.

Further, we examined the scope of this reaction for synthesis of various substituted isoxazoles using similar reaction conditions (Figure 5). Phenyl, p-tolyl and n-tolyl aldoximes gave good yields, irrespective of the location of alkyl substituent (examples 6f, 6g, 6i, 6k, 6l, 6n and 6p). Similarly, the electron-rich styrenes (examples 6h, 6i and 6p) and halo-substituted styrenes gave good yields. Among heteroaryl aldoximes, the pyridine aldoxime produced corresponding isoxazoline 6m in good yield, whereas indole aldoxime produced corresponding isoxazoline 6q, comparatively in a lesser yield.

Figure 5. Scope of the reaction for synthesis of isoxazoles. Reagents and conditions: aldoxime (1 equiv.), styrene (1.2 equiv.), DBU (1 equiv.), NCS (1.2 equiv.), DMF, 1-8 h, 63-85%. Reaction time: 1 h for 6b and 6d; and 8 h for other examples.

Next, we sought to explore the observed finding of one-pot 1,3-dipolar cycloaddition reaction followed by ring chlorination to produce chlorinated isoxazoles and isoxazolines (Figure 6). For this, we thought to use higher equivalents of NCS than the required amount, to get increased yields of chlorinated products. To our surprise, when aldoxime 1a was treated with phenylacetylene 3a in presence of 2.2 equivalents of NCS and 1 equiv of DBU, exclusively the chloro-substituted product 7a was obtained (88% yield). Similarly, we prepared other chlorinated isoxazoles 7b, 7c, 7f, 7g and 7j using higher equivalents of NCS. The tandem one-pot, 1,3-dipolar cycloaddition followed by regioselective chlorination also worked well for synthesis of chlorinated isoxazolines (Figure 6; examples 7d, 7e and 7h). In case of furan-2-aldoxime, the isoxazole product 7g was formed in good yield (90%), however lower yield (60%) was obtained for isoxazoline product 7h. In case of indole-3-aldoxime and pyridine-2-aldoxime, ring chlorination product was not formed even after using higher equivalents of NCS. It is noteworthy to mention that the furyl compound 7g has a structural similarity with reported COX-1 inhibitor (structure B, Figure 1).
Next, we sought to investigate the mechanistic sequence of 1,3-dipolar cycloaddition and ring chlorination (Figure 7) reactions using LCMS analysis. For this, we first performed reaction of aldoxime 1a with phenylacetylene 3a under optimized reaction conditions (1.2 equiv NCS). The LCMS chromatogram after 30 min reaction time (figure 7a) indicated formation of desired product 4a (tR = 9.4 min). However, with the use of 2.2 equiv NCS, the LCMS chromatogram after 40 min indicated formation of chlorinated isoxazole 7a (tR = 10.5 min) along with product 4a (tR = 9.4 min). Further, when this reaction was monitored after 8 h, the LCMS chromatogram showed solely the formation of chlorinated product 7a. This study indicated that the chlorination reaction must be occurring after formation of isoxazole skeleton.

In order to further understand the other possibility of first chlorination and then 1,3-dipolar cycloaddition, we treated aldoxime 1a with 2.2 equiv of NCS and stirred for 8 h, which indicated formation of ring-chlorinated aldoxime only in 15%, which further indicates that in one-pot tandem protocol, chlorination occurs after 1,3-dipolar cycloaddition reaction.

In conclusion, we have developed a new metal-free DBU-promoted synthesis of isoxazole and isoxazolines from aldoximes. Additionally, an interesting one-pot protocol for tandem 1,3-dipolar cycloaddition followed by regioselective ring chlorination has been reported. This methodology was applied to one-pot synthesis of 4-chloro-furyl-isoxazole and pyridine-isoxazole scaffold which are reported to possess potent biological activities.

**Experimental Section**

*General procedure for preparation of isoxazoles 4a-4l, isoxazolines 6a-6q and chlorinated isoxazole/isoxazoline products 7a-7h.* To the stirred solution of aldoximes (100 mg, 1 equiv.) in DMF (3 ml) was added N-chlorosuccinimide (1.2 or 2.2 equiv.) at room temperature and reaction was stirred for 0.5-1 h. Then, DBU (1 equiv.) and styrenes or alkynes (1.2 equiv.) were added and reaction was further stirred for 1-8 h. After completion of the reaction (confirmed by TLC), chilled water (20 ml) was added and product was extracted with EtOAc (3 × 10 ml). The organic layer was collected, dried on anhydrous sodium sulphate and solvent was evaporated on rotary evaporator to get the crude product. The crude product was purified by silica gel (#100-200) column chromatography using 2 to 20% EtOAc:hexane to get pure isoxazoles 4a-4l, isoxazolines 6a-6q or chlorinated isoxazole/isoxazoline products 7a-7h in 50-90% yield. The spectral data of representative compounds 4a, 6a and 7a is shown here. Spectral data of other compounds 4b-4l, 6b-6q and 7b-7h is provided in ESI.

**4-(5-Phenylisoxazol-3-yl) phenol (4a).** White solid; yield 80%; m. p. 187 – 189 °C ; 1H NMR (400 MHz, CDCl3, ppm): δ 7.83 (dd, J = 4, 8Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.47 (m, 3H), 6.95 (d, J = 8 Hz, 2H), 6.78 (s, 1H); 13C NMR (CDCl3, ppm): δ 170.0, 162.9, 158.8, 130.2, 128.9, 128.2, 127.2, 125.7, 121.0, 115.7, 97.3; IR (CHCl3): νmax 2383, 1095, 1017 cm⁻¹; ESI-MS: m/z 238.0864 calcd for C15H12NO+H⁺ (238.0864).

**3,5-Diphenyl-4,5-dihydroisoxazole (6a).** White solid; yield 85%; m. p. 72-74 °C; 1H NMR (400 MHz, CDCl3, ppm): δ 7.70 (dd, J = 4, 8Hz, 2H), 7.30- 7.42 (m, 8H), 5.78 (s, 1H); 13C NMR (CDCl3, ppm): δ 156.1, 140.9, 130.2, 129.4, 128.8, 128.2, 126.7, 125.9, 82.6, 43.2; IR (CHCl3): νmax 1619, 1334, 2920, 1730, 1446, 1352, 1120, 893, 751, 686 cm⁻¹; ESI-MS: m/z 224.10 [M+H⁺]; HRMS: m/z 224.1048 calcd for C15H12NO+H⁺ (224.1070).

**2-Chloro-4-(5-phenylisoxazol-3-yl)phenol (7a).** White solid; yield 88%; m. p. 193-196 °C; 1H NMR (400 MHz, CDCl3, ppm): δ 7.89 (d, J = 4.1, 1Hz, 1H), 7.82-7.84 (m, 2H), 7.68-7.71 (m, 1H), 7.47-7.50 (m, 3H), 7.13 (d, J = 8 Hz, 1H), 6.77 (s, 1H), 5.78 (s, 1H); 13C NMR (CDCl3, ppm): δ 170.3, 161.9, 154.4, 130.3, 128.9, 128.3, 127.1, 126.3, 125.7, 121.0, 116.7, 97.2; IR (CHCl3): νmax 3346, 2922, 2851, 1540, 1422, 1019 cm⁻¹; ESI-MS: m/z 272.04 [M+H⁺]; HRMS: m/z 272.0481 calcd for C15H12ClNO2+H⁺ (272.0473).

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**References and notes**


