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Harnessing the TEMPO catalyzed aerobic oxidation for Machetti–De Sarlo reaction towards sustainable synthesis of isoxazole libraries

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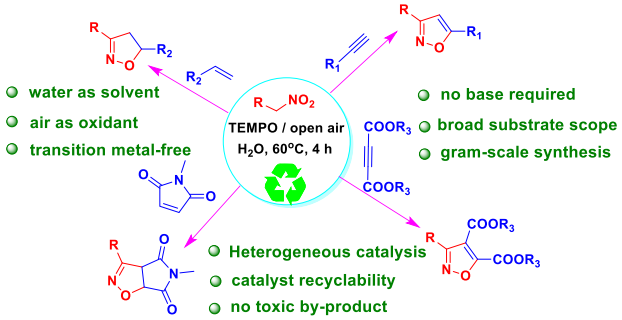


ABSTRACT: A practical synthesis of isoxazole/isoxazoline derivatives via Machetti–De Sarlo reaction under sustainable conditions has been accomplished. This protocol involves the use of readily available TEMPO to catalyze the cyclocondensation of primary nitroalkanes with alkynes/alkenes to afford a library of isoxazole/isoxazoline products. From an eco-benign perspective, notable advantages of this method are (i) water as solvent, (ii) air as oxidant, (iii) transition metal-free, (iv) no base required, (v) no toxic by-product, (vi) no need of solvent extraction, (vii) diverse substrate scope, (viii) high chemical yields, (ix) excellent chemo- and regioselectivity, (x) short reaction time, (xi) gram-scale synthesis, (xii) extension to heterogeneous version and (xiii) catalyst recyclability. For these reasons, the developed method is appropriate for safe laboratory use and can be expected to inspire the progress of TEMPO based organocatalysis for the preparation of isoxazole/isoxazoline moieties in an environmentally benign fashion.

INTRODUCTION

Designing practical and eco-benign synthetic methods from simple precursors with no formation of toxic by-products is of substantial importance in sustainable chemistry.[1-5] In a similar vein, chemical transformations performed at aerobic conditions offers an added advantage from a green chemistry viewpoint.[6-8] On the other hand, chemical processes performed in water has an extensive advantage of both environmental compatibility as well as less expensiveness compared to organic solvents.[9] Thus, there has been increasing recognition of water as an attractive medium for numerous organic transformations.[10-12] To this end, a plethora of heterocycles such as furans, pyridines, quinolines, indoles, triazines, acridines, pyrazines and pyrimidines have been synthesized in aqueous media.[13-22] Likewise, isoxazoles are five-membered nitrogen/oxygen containing heterocycles commonly found in variety of pharmacologically active natural products, clinical drugs and lead compounds (Fig 1, top panel).[23-27] With no confinement to biology, they also finds extensive application as building blocks in synthetic chemistry[28, 29] and as organic materials in optoelectronics.[30, 31] Because of its unique physical properties, the construction of this heterocyclic nucleus has continued to attract the research community for decades.[32-34] The most frequently used strategy for isoxazole preparation involves [3+2] cycloaddition of alkynes with nitrile oxides or through the reaction between hydroxyl amine and a three-carbon component.[35] Within these methods, the intermolecular cyclization between primary nitro compounds and alkynes have received wide attention, because it builds up isoxazole core in a straightforward manner without requiring additional synthetic steps (Fig. 1, bottom panel). However, this chemistry requires a strong dehydrating agent (usually an acylating agent or base) in stoichiometric proportion and thus possess deleterious effect (eq. 1).[36-41] A progressive work by Machetti and De Sarlo circumvented this limitation by utilizing water as medium.[42,43] These particular methodology is quite advantageous for the construction of both isoxazole as well as isoxazoline frameworks with good functional group tolerance, yet with the requirement of catalytic amount of base (DABCO or NaOH), long reaction time and moderate yields (eq. 2). The same team in another endeavor disclosed that similar reaction works under Cu(II)/base catalysis.[44] Despite the broad substrate scope, some minor shortcomings of this method include low chemical yields, longer reaction time, regioselective issues and chloroform as solvent (eq. 3). From the background of synthetic application of Machetti-De Sarlo reaction[45-47], it is quite obvious that a comprehensive green approach addressing the aforementioned issues for the direct synthesis of isoxazoles is need of the hour. At this juncture, it is pertinent to mention that

organic-nitroxyls catalyzed aerobic oxidation offers perfect platform for green synthesis.[48] Especially, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) possess practical advantages owing to their water-soluble nature, non-toxicity and less expensiveness which allows its use as an ideal green oxidant for organic transformations.[49-51] As part of our research direction on sustainable synthesis[52-56] and energy,[57, 58] we envisioned a green chemical approach for the synthesis of isoxazoles synthesis under TEMPO catalysis. Our working hypothesis is that TEMPO could oxidize the nitro to nitrile oxide *in situ* suitable for a sequential 1,3-dipolar cycloaddition reaction with alkynes (eq 4). To the best of our knowledge, this approach features several green advantages compared to other procedures and the relevant results are disclosed in this paper.

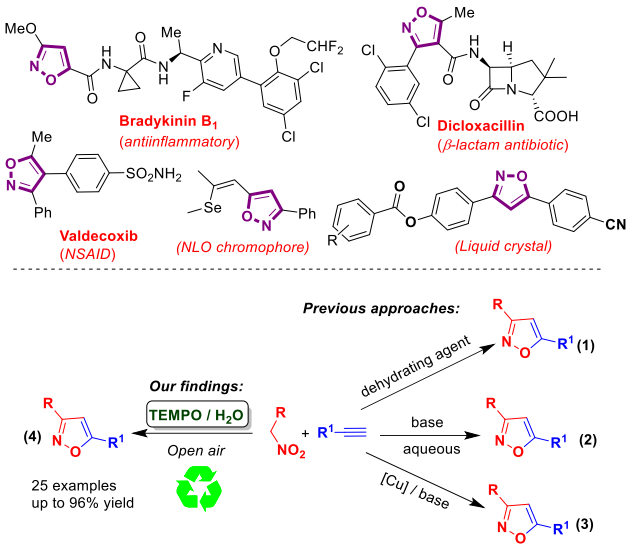
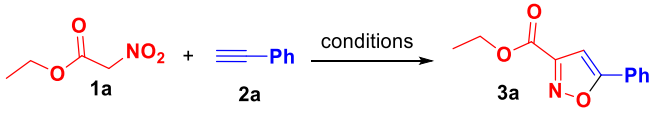


Fig. 1 Pharmacologically active isoxazole molecules (top panel); Cyclocondensation Pathways for the synthesis of isoxazole scaffolds (bottom panel)

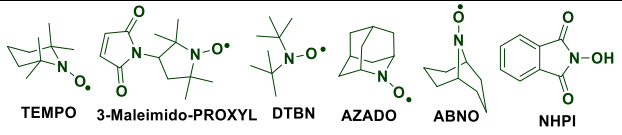
RESULTS AND DISCUSSION

Based on our previous experience of using TEMPO catalysis for organo-click reactions,[55] we intended to use the same catalyst for the present work. We initiated our preliminary investigation through the prototype synthesis of 3,5-disubstituted isoxazole (**3a**) from ethyl nitroacetate (**1a**, 1.5 mmol), phenylacetylene (**2a**, 1.0 mmol) and TEMPO (10 mol%) in water (2 mL). At the outset, a room temperature (30 °C) reaction afforded only a moderate yield (35%) of **3a** even after 24 h (entry 1). To our delight, the reaction proceeded well after a double-fold increase in temperature (60 °C) to form **3a** in 81% yield (entry 2). Though, this chemistry also works equally in chloroform, we preferred to use water on the grounds of green chemistry. Based on these initial observations, we quickly arrived at using TEMPO as catalytic source for further optimization. Thus, reducing the reaction time to 8 and 4 h slightly improvised the yield to 86 and 96% respectively (entries 3 and 4). Avoiding water to achieve solvent-free conditions had a negative influence on the yield which could be attributed to the inefficient mixing of reactants under neat condition (entry 5). Moreover, decreasing the catalytic loading from 10 to 5 mol% required longer reaction time for the completion of reaction with notable diminution in yield (entry 6). It is to be remembered that all the tested reactions were performed under open-flask conditions, which could result in the participation of atmospheric dioxygen to effect catalytic-aerobic oxidation. Therefore, two controlled experiments under the atmosphere of O_2 and N_2 were carried out separately. In case of O_2, the yield was quite similar to that obtained under open atmosphere (entry 7). In contrast, the yield was lowered to a greater extent under N_2 condition (entry 8). These two investigations suggest the possible role of O_2 acting as co-oxidant in regenerating the TEMPO. To compare the efficacy with TEMPO, other related dialkyl nitroxides were scrutinized under similar conditions (as per entry 4). The results of which revealed that the reaction with 3-maleimido-PROXYL (2,2,5,5-tetramethylpyrrolidine-*N*-oxyl), a pyrrolidine-based nitroxide is sluggish to afford poor yield of product (entry 9). Likewise, structurally simple DTBN (di-*tert*-butyl nitroxide) afforded only moderate yield (entry 10). However, the bicyclic variants such as 2-azaadamantane *N*-oxyl (AZADO) and 9-azabicyclononane-*N*-oxyl (ABNO) afforded products with yields comparable to that of TEMPO (entries 11 and 12). Despite the good catalytic potential of these nitroxyls, their cost is too high compared to TEMPO (ABNO; 250 mg = $ 139, AZADO; 250 mg = $ 254, TEMPO; 1g = $ 21, Sigma-Aldrich). Avoiding high cost is of considerable importance from the perspective of green engineering,[59] thus using TEMPO is quite advantageous compared to other expensive nitroxyls. *N*-hydroxyphthalimide (NHPI),[60] a much cheaper and widely used organocatalyst in aerobic process also produced poor yield of **3a** (entry 13). Concerning the overall picture, we validated the best condition as: heating a mixture of alkyne (1.0 mmoL), nitroalkane (1.5 mmoL) and TEMPO (10 mol%) in water (2 mL) at 60 °C for 4 h under open-air conditions. Under this condition, an array of substrates undergoes the reaction smoothly and generated the isoxazole products in good to excellent yields (Chart 1).

Table 1 Optimization studies tested on the synthesis of **3a**[a]



Entry	Organic-nitroxyl (mol%)	T (°C)	time (h)	Additive	Yield (%)[b]
1	TEMPO (10)	30	24	air	35
2	TEMPO (10)	60	12	air	81
3	TEMPO (10)	60	8	air	86
4	TEMPO (10)	60	4	air	96
5[c]	TEMPO (10)	60	4	air	49
6	TEMPO (5)	60	24	air	71
7	TEMPO (10)	60	4	O_2	96
8	TEMPO (10)	60	4	N_2	18
9	3-Maleimido-PROXYL (10)	60	4	air	20
10	DTBN (10)	60	4	air	37
11	AZADO (10)	60	4	air	95
12	ABNO (10)	60	4	Air	91
13	NHPI (10)	60	4	Air	28



[a]All tested reactions were performed using 1.5 mmol of **1a** and 1.0 mmol of **2a**; [b]Isolated yield of product **3a**; [c]Solvent-free condition

As the first part of substrate variation, different terminal acetylenes such as arylalkynes, propargyloxy aromatics and aliphatic alkynes were reacted with ethyl nitroacetate under the optimized conditions. All of these alkynes furnished the desired 3,5-disubstituted isoxazoles (**3a, 3b, 3d, 3e** and **3u**) in excellent yields (>90 %). However, products (**3c, 3f** and **3g**) derived from alkynes possessing deactivating substituents like -C_6F_5, -NO_2 and -CN were obtained in slightly reduced yields (85-89%), which could be reasoned to the created electron deficiency around the alkyne unit. However, other substrates including benzoylnitromethane and methyl nitroacetate reacts with equal efficiency towards electronically distinguishable alkynes as exemplified by the excellent chemical yields (90-96%) of **3h-3s**. The overall process is regiocontrolled, since 3,5-disubstituted isoxazoles are formed as sole isomers with no formation of theoretically possible 3,4-disubstituted isomers. It is noteworthy to mention, that alkyne substrates having silyl and amide tether tolerated well under the standard reaction conditions to form the functionalized isoxazoles **3v** and **3w** respectively. The optimized conditions were also found to be amenable to alkynes holding hydroxyl functionality (**3x** and **3y**). Notably, **3x** having a primary alcohol was isolated as the sole product without over-oxidization *via* TEMPO catalysis, signifying the mildness of our oxidative conditions. Instead of nitro derivatives possessing active methylene group, a test reaction with CH_3NO_2 completely failed to proceed. This could be because of the slow deprotonation of CH_3NO_2 under aqueous condition (*p*Ka = 11).[61] Nevertheless, the scope of the current green methodology is quite comprehensive to accommodate a wide range of substrates of different electronic nature. In terms of simplicity and practicality, the developed protocol seems to be superior compared to some of the literature precedents for the combinatorial synthesis of isoxazoles.[62-67] The structure of all products was thoroughly characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. As an illustrative example, the FT-IR of **3k** displayed an absorbance band at 1660 cm^{-1} characteristic of the C=N stretching of the isoxazole nucleus. In ^{1}H NMR recorded as $CDCl_3$ solution, two singlets at δ 5.21 and 6.87 ppm corresponds to the protons of the -OCH_2- group and C4-H of the isoxazolyl ring respectively. In ^{13}C NMR spectrum, sharp peaks at δ 61.8 and 185.4 ppm individually approves to the -OCH_2- and C=O carbons. A peak at δ 104.5 ppm is typical of the C4 carbon of the isoxazolyl ring. HRMS analysis exhibited a peak at *m/z*(obs.) = 297.0810 corresponds to the molecular ion $[M]^+$ is in good agreement with the expected *m/z*(expd.) = 297.0801. Finally, X-ray diffraction analysis of single crystals obtained after recrystallization from chloroform solution unambiguously established the structure of **3k** (CCDC 1813138).[68]

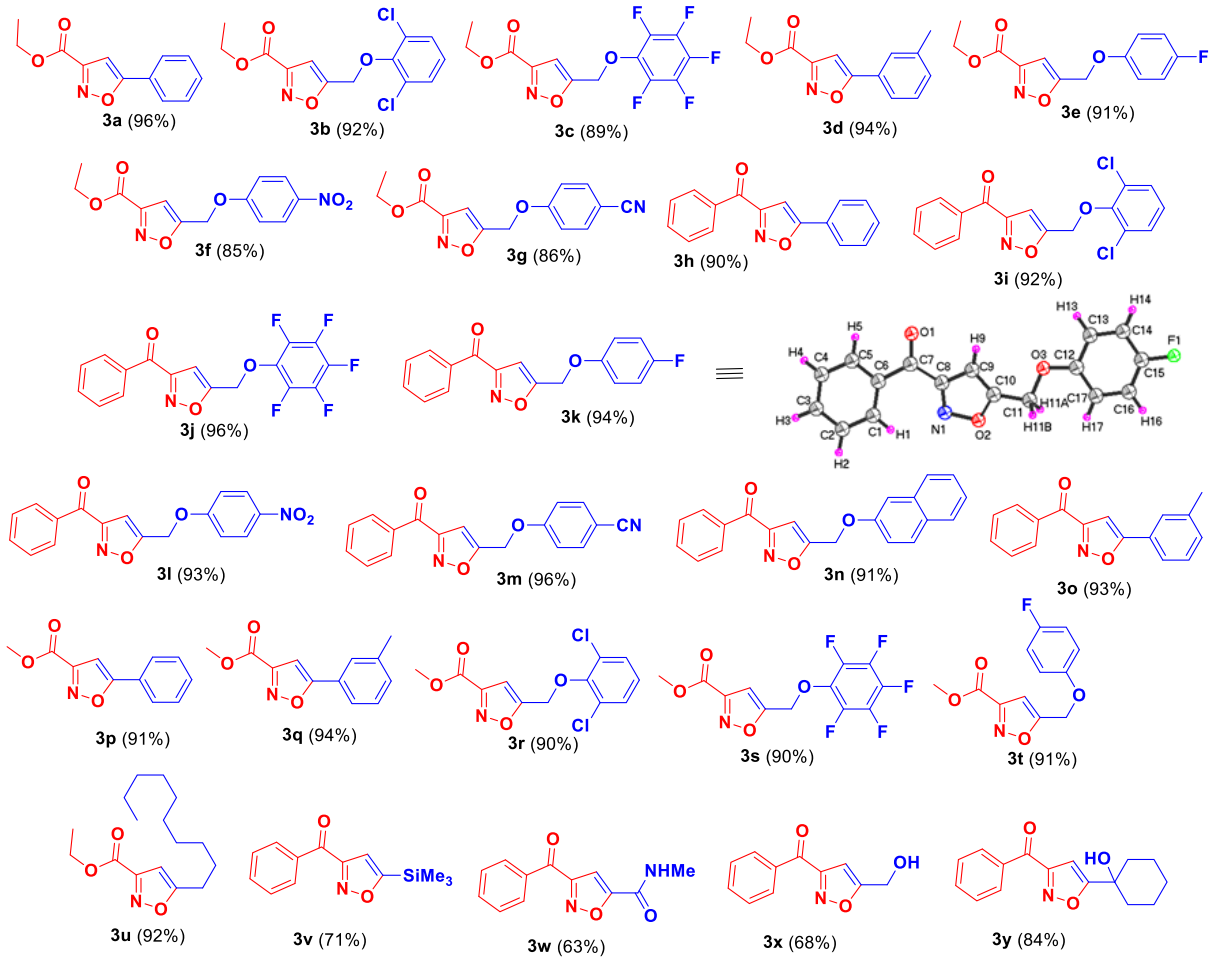
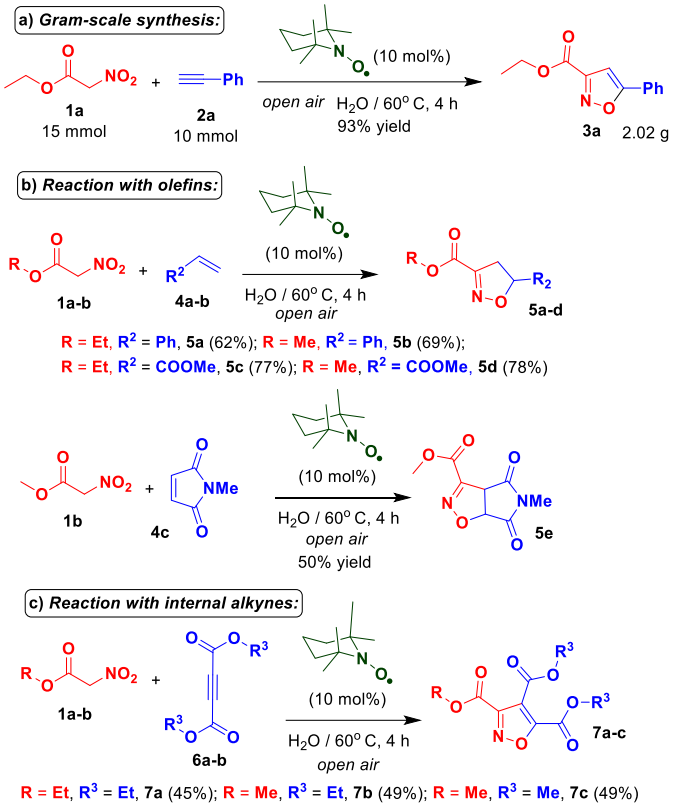
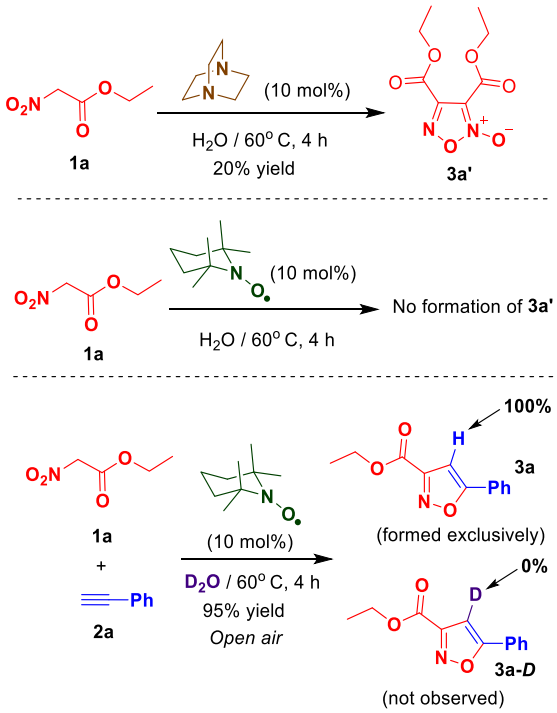


Chart 1 Synthesized isoxazole libraries (**3a-3y**) in aerobic oxidative conditions under TEMPO catalysis



Scheme 1 a) Scale-up reaction; b) Synthetic elaboration to olefins; and c) internal alkynes

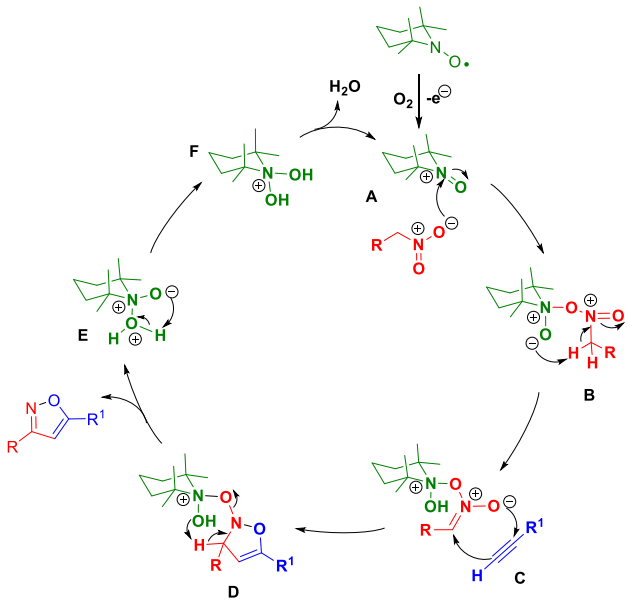
To showcase the synthetic applicability of our procedure, a gram-scale synthesis of **3a** in 2.02 g was accomplished (Scheme 1a). To further explore the generality of the current protocol, olefins instead of alkynes were reacted with ethyl/methyl nitroacetate **1a-b** under similar conditions (Scheme 1b). Indeed, the reaction worked well with styrene (**4a**) and methyl acrylate (**4b**) to give Δ^2-isoxazolines (**5a-d**) in moderate to good yield of 62, 69, 77 and 78% respectively. Nevertheless, this slightly reduced yield could possibly because of the lesser electron density of the sp^2-carbon compared to the sp^3-carbon of alkyne surrogates. In a similar manner, cyclic olefin in the form of N-methylmaleimide (**4c**) also undergoes cyclo-condensation with **1a** affording the bicyclic isoxazoline (**5e**) in 50% yield. It is appropriate to mention that Δ^2-isoxazolines tend to undergo oxidation to the corresponding isoxazoles.[69-71] However, the isoxazolines (**5a-e**) formed does not undergo *in situ* oxidation to isoxazoles clearly signifies the mild nature of our reaction conditions. On the other hand, symmetrical internal alkynes such as diethyl acetylenedicarboxylate (**6a**) and dimethyl acetylenedicarboxylate (**6b**) yielded the corresponding 3,4,5-trisubstituted isoxazole (**7a-c**) in moderate, yet synthetically acceptable yields (Scheme 1c). Here too, the reduced electron density at the alkyne carbons by electron withdrawing -COOR[3] groups is reasoned to the low chemical yield.[72]



Scheme 2 Control experiments for mechanistic understanding

To gain insight into the mechanism, it is noteworthy to mention that the nitrile-oxide mechanism is validated in an event of intermolecular addition–elimination of ethyl nitroacetate (**1a**) to

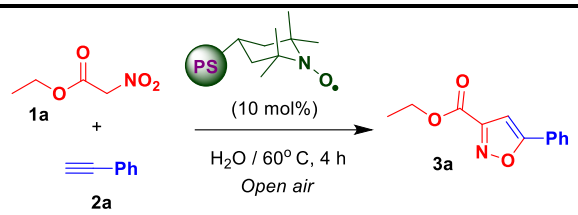
form 3,4-bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide (**3a'**) under DABCO catalysis following the literature procedure (Scheme 2, top panel).[44, 73] When we attempted the same reaction using TEMPO instead of DABCO leads to the quantitative recovery of starting material **1a** with no formation of **3a'** (Scheme 2, middle panel). This observation clearly excludes the possibility of generation of nitrile oxide intermediates during the reaction course, therefore, must involve a different mechanism under TEMPO conditions. When the reaction between **1a** and **2a** was carried out at standard conditions by replacing H_2O with D_2O, no deuterium incorporated product (**3a-*D***) was observed and only **3a** was obtained (Scheme 2, bottom panel). Since none of deuterium incorporation was detected in the product, it attributes to the non-intervention of water *via* proton exchange in the reaction. It is also to be remembered that the yield of **3a** is significantly reduced to 18% under N_2 atmosphere (as per Table 1, entry 8), which obviously testifies the involvement of O_2 in the reaction. From all the above remarks from control experiments, a tentative mechanism was proposed (Scheme 3). According to which, TEMPO undergoes a one electron oxidation in the presence of O_2 to form *N*-oxoammonium ion **A**.[74] This was followed by the nucleophilic attack of oxygen of -NO_2 group to the quaternary nitrogen of **A** to generate intermediate **B**. Subsequently, the oxygen anion of **B** abstracts the α-hydrogen to form a nitrone-type 1,3-dipole intermediate **C**. As a consequence, the latter undergoes cycloaddition with alkyne to form the cyclic intermediate **D**. Another abstraction of α-hydrogen leads to the formation of isoxazole along with intermediate **E**. Proton transposition of latter results in intermediate **F** suitable for further dehydration to regenerate TEMPO.



Scheme 3 Proposed mechanism for the formation of isoxazoles under TEMPO catalyzed aerobic oxidation

At this point of our investigation, we became interested on the heterogeneous version of our chemistry, because of the foreseen advantage of catalyst recovery after the reaction. Hence, we chose commercially available polymer immobilized TEMPO (PS-TEMPO, 1.0 mmol/g loading) for the model reaction (Table 2). Gratifyingly, the use of PS-TEMPO under the optimized conditions resulted in **3a** in an excellent yield of 95%, which is as comparable to the yield from free TEMPO (96%). Comparatively, the same product by DABCO catalysis[42] was reported to be obtained in 69% only after 18 h, thus signifies the efficiency of the developed protocol. After completion of the reaction, PS-TEMPO was removed from the reaction mixture by simple centrifugation, washed with water followed by pre-cooled ethanol. Subsequent drying at 80 °C for 2 h affords the recovered PS-TEMPO, which can be used directly for more catalytic runs without further activation. The recuperated PS-TEMPO can be used up to six catalytic cycles with almost negligible decrease in yield and conversion after each cycle. Accordingly, the catalyst recyclability studies evidently highlight the attractiveness of the developed protocol from the viewpoint of green chemistry.

Table 2 Recycling experiments tested on heterogeneously immobilized TEMPO[a]



Catalytic cycle	Catalyst recovery (%)	Conversion (%)[b]	Isolated yield (%)
1	100	>99	95
2	100	>99	94
3	99	97	92
4	99	97	91
5[c]	98	95	91
6	98	94	90

[a]1.5 mmol of **1a**, 1.0 mmol of **2a**, 10 mol% of PS-TEMPO (100 mg of 1.0 mmol/g loading) and water (2 mL) at open air condition; [b]Conversion monitored by crude NMR analysis and >99% indicates no remaining of **2a.**

In summary, a simple and safe laboratory procedure for the preparation of isoxazoles/isoxazolines by adopting Machetti−De Sarlo chemistry from commercially viable and inexpensive starting materials were accomplished. The key feature of this chemistry is the use of catalytic amounts of TEMPO as non-toxic oxidant to promote the oxidative cycloaddition step in aqueous medium. The practical feasibility of this method is validated through the synthesis of structurally diverse isoxazole derivatives. From the perspective of synthetic chemistry, the advantages include high chemical yields, wide substrate scope, gram-scale synthesis, excellent regioselectivity, operational simplicity and short reaction time. The process also encompasses several eco-friendly aspects such as open-air conditions, water as solvent, no toxic by product, no solvent extraction, base and transition-metal free. Another sustainable advantage is the ease with which the reaction works equally well in heterogeneous conditions in presence of polymer supported TEMPO. In the latter case, the heterogeneous catalyst can be easily recuperated and reused for six catalytic cycles without significant loss in activity. On a whole, the present study demonstrates the dexterity of TEMPO as green catalytic oxidant for the synthesis of isoxazole libraries under green conditions. The application of

this sort of chemistry for the sustainable synthesis of other hetero- and carbocycles are actively underway in our laboratory.

EXPERIMENTAL SECTION

General methods and materials

All chemicals and solvents were purchased from Sisco Research Laboratories and Alfa Aesar Pvt. Ltd. PS-TEMPO (100-200 mesh, 1.0 mmol/g loading, 1% cross-linked with divinylbenzene) was purchased from Sigma-Aldrich Pvt. Ltd. Infrared (IR) spectra for all compounds were recorded as neat by Attenuated Total Reflectance (ATR) mode on a JASCO 6300 FTIR spectrometer. Column chromatography was performed using thick-walled glass columns along with a mixture of petroleum ether and ethyl acetate on silica gel (100-200 mesh, SRL, India). The relative proportions of solvents in chromatography solvent mixtures refer to the volume to volume ratio. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualized with iodine spray (10% w/w I_2 in silica gel), UV light (λ = 254 and 365 nm) and alkaline $KMnO_4$ solution.All melting points were measured on open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) using Bruker spectrometer (^1H NMR: 400 and 500 MHz; ^{13}C NMR: 100 and 125 MHz). Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as an internal standard and are expressed in parts per million (ppm). The number of protons (n) for a given resonance is indicated as nH. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (*J*) are given in hertz (Hz). Mass spectra were recorded on a JEOL GC Mate (II) using electron impact ionization (EI-Quadrupole) and Micromass (ESI-QTOF) spectrometer technique.

Typical procedure for the preparation of isoxazoles (3a-3u):

A mixture of nitroalkane **1a-c** (1.5 mmoL), alkyne **2a-m** or **6a-b** (1.0 mmoL), TEMPO (10 mol%) and water (2 mL) were heated to 60 °C (oil bath) with vigorous stirring in an open tube for 4 h. Upon completion of the reaction as indicated by TLC, water was removed under reduced pressure. To this residue, ethyl acetate (5 mL) was added and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to obtain the crude product, which was further purified by a short silica gel flash chromatography to obtain pure product of **3a-3y** and **7a-7c**.

Typical procedure for the preparation of isoxazolines (5a-5c):

A mixture of nitroalkane **1a-b** (1.5 mmoL), styrene/methylacrylate/N-methylmaleimide **4a-c** (1.0 mmoL), TEMPO (10 mol%) and water (2 mL) was heated to 60 °C (oil bath) with vigorous stirring in an open tube for 4 h. Upon completion of the reaction as indicated by TLC, water was removed under reduced pressure. To this residue, ethyl acetate (5 mL) was added and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to obtain the crude product, which was further purified by a short silica gel flash chromatography to obtain pure product of **5a-5e**.

Ethyl 5-phenylisoxazole-3-carboxylate **(3a).**[76] White solid; 205 mg (96%), R_f = 0.56 (20% Ethylacetate : n-Hexane); Mp 47-49 °C (lit.[76] 48-49 °C); FT-IR (neat): υ = 1726, 1613, 1476, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.82-7.80 (m, 2H), 7.49-7.48 (m, 3H), 6.93 (s, 1H), 4.48 (q, *J* = 8.0 Hz, 2H), 1.44 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 160.0, 156.9, 130.8, 129.1, 126.7, 125.9, 99.9, 62.2, 14.2.

Ethyl 5-((2,6-dichlorophenoxy)methyl)isoxazole-3-carboxylate **(3b)**. White solid; 288 mg (92%), R_f = 0.47 (20% Ethylacetate : n-Hexane); Mp 79-81 °C; FT-IR (neat): υ = 1765, 1628, 1489, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (d, *J* = 8.0 Hz, 2H), 7.09-7.05 (m, 1H), 6.87 (s, 1H), 5.22 (s, 2H), 4.46 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.1, 159.7, 156.5, 150.2, 129.5, 129.2, 126.2, 104.9, 64.8, 62.3, 14.2; HRMS (EI-Quadrupole): *m/z* = 315.0064, calcd. for $C_{13}H_{11}Cl_2NO_4$ (M^+): 315.0065.

Ethyl 5-((perfluorophenoxy)methyl)isoxazole-3-carboxylate **(3c)**. White solid; 135 mg (89%), R_f = 0.44 (20% Ethylacetate : n-Hexane); Mp 62-64 °C; FT-IR (neat): υ = 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.83 (s, 1H), 5.32 (s, 2 H), 4.46 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 159.4, 156.6, 143.1, 140.5, 139.3, 136.8, 105.2, 66.1, 62.5, 14.1; HRMS (EI-Quadrupole): *m/z* = 337.0371, calcd. for $C_{13}H_8F_5NO_4$ (M^+): 337.0373.

Ethyl 5-(m-tolyl)isoxazole-3-carboxylate **(3d)**. White solid; 375 mg (94%), R_f = 0.61 (20% Ethylacetate : n-Hexane); Mp 56-58 °C; FT-IR (neat): υ = 1762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62-7.59 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 4.47 (q, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.44 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 160.1, 156.9, 138.9, 131.6, 129.0, 126.6, 126.5, 123.1, 99.8, 62.2, 21.4, 14.2; HRMS (EI-Quadrupole): *m/z* = 231.0894, calcd. for $C_{13}H_{13}NO_3$ (M^+): 231.0895.

Ethyl 5-((4-fluorophenoxy)methyl)isoxazole-3-carboxylate **(3e)**. White solid; 320 mg (91%), R_f = 0.41 (20% Ethylacetate : n-Hexane); Mp 63-65 °C; FT-IR (neat): υ = 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.02-6.98 (m, 2H), 6.92-6.88 (m, 2H), 6.74 (s, 1H), 5.17 (s, 2H), 4.44 (q, *J* = 8.0 Hz, 2H), 1.41 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 159.6, 158.0 (d, *J* = 238.8 Hz), 156.6, 153.6 (d, *J* = 2.2 Hz), 116.2 (d, *J* = 23.2 Hz), 116.1 (d, *J* = 8.1 Hz), 104.0, 62.3, 61.8, 14.1; HRMS (EI-Quadrupole): *m/z* = 265.0752, calcd. for $C_{13}H_{12}FNO_4$ (M^+): 265.0750.

Ethyl 5-((4-nitrophenoxy)methyl)isoxazole-3-carboxylate **(3f)**. White solid; 280 mg (85%), R_f = 0.24 (20% Ethylacetate : n-Hexane); Mp 121-123 °C; FT-IR (neat): υ = 1762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.26-8.23 (m, 2H), 7.07-7.05 (m, 2H), 6.82 (s, 1H), 5.32 (s, 2H), 4.46 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 168.2, 162.2, 159.5, 156.7, 142.5, 126.1, 114.8, 104.6, 62.5, 61.2, 14.1; HRMS (EI-Quadrupole): *m/z* = 292.0695, calcd. for $C_{13}H_{12}N_2O_6$ (M^+): 292.0695.

Ethyl 5-((4-cyanophenoxy)methyl)isoxazole-3-carboxylate **(3g)**. White solid; 300 mg (86%), R_f = 0.19 (20% Ethylacetate : n-Hexane); Mp 112-114 °C; FT-IR (neat): υ = 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65-7.62 (m, 2H), 7.05-7.02 (m, 2H), 6.79 (s, 1H), 5.27 (s, 2H), 4.46 (q, *J* = 8.0 Hz, 2H), 1.42 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ

(ppm) 168.4, 160.6, 159.5, 156.7, 134.3, 118.7, 115.4, 105.6, 104.5, 62.5, 60.9, 14.1; HRMS (EI-Quadrupole): *m/z* = 272.0799, calcd. for $C_{14}H_{12}N_2O_4$ (M^+): 272.0797.

Phenyl (5-phenylisoxazol-3-yl)methanone **(3h)**.[44] White solid; 220 mg (90%), R_f = 0.76 (20% Ethylacetate : n-Hexane); Mp 78-80 °C (lit.[44] 84-85 °C); FT-IR (neat): υ = 1665, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.36-8.34 (m, 2H), 7.86-7.84 (m, 2H), 7.66-7.64 (m, 1H), 7.56-7.49 (m, 5H), 7.05 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.8, 170.8, 162.5, 135.8, 134.1, 130.8, 130.7, 129.2, 128.6, 126.7, 126.0, 100.3.

(5-((2,6-Dichlorophenoxy)methyl)isoxazol-3-yl)(phenyl)methanone **(3i)**. White solid; 159 mg (92%), R_f = 0.66 (20% Ethylacetate : n-Hexane); Mp 139-141 °C; FT-IR (neat): υ = 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32-8.29 (m, 2H), 7.67-7.63 (m, 1H), 7.55-7.51 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.08-7.06 (m, 1H), 6.96 (s, 1H), 5.26 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.5, 168.0, 161.9, 150.3, 135.7, 134.1, 130.7, 129.6, 129.2, 128.6, 126.1, 105.3, 64.7; HRMS (EI-Quadrupole): *m/z* = 347.0114, calcd. for $C_{17}H_{11}Cl_2NO_3$ (M^+): 347.0116.

(5-((Perfluorophenoxy)methyl)isoxazol-3-yl)(phenyl)methanone **(3j)**. White solid; 160 mg (96%), R_f = 0.68 (20% Ethylacetate : n-Hexane); Mp 64-65 °C; FT-IR (neat): υ = 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31-8.28 (m, 2H), 7.69-7.64 (m, 1H), 7.55-7.52 (m, 2H), 6.94 (s, 1H), 5.36 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.1, 166.9, 161.9, 143.0, 140.7, 139.3, 136.8, 135.4, 134.3, 132.1, 130.7, 128.7, 105.6, 66.1; HRMS (EI-Quadrupole): *m/z* = 369.0422, calcd. for $C_{17}H_8F_5NO_3$ (M^+): 369.0424.

(5-((4-Fluorophenoxy)methyl)isoxazol-3-yl)(phenyl)methanone **(3k)**. White solid; 187 mg (94%), R_f = 0.65 (20% Ethylacetate : n-Hexane); Mp 99-101 °C; FT-IR (neat): υ = 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31-8.29 (m, 2H), 7.68-7.63 (m, 1H), 7.54-7.51 (m, 2H), 7.04-6.99 (m, 2H), 6.95-6.92 (m, 2H), 6.87 (s, 1H), 5.21 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.4, 168.6, 161.9, 157.9 (d, *J* = 238.7 Hz), 153.7 (d, *J* = 2.2 Hz), 135.6, 134.2, 130.7, 128.6, 116.2 (d, *J* = 23.2 Hz), 116.1 (d, *J* = 8.0 Hz), 104.5, 61.8; HRMS (EI-Quadrupole): *m/z* = 297.0810, calcd. for $C_{17}H_{12}FNO_3$ (M+): 297.0801.

(5-((4-Nitrophenoxy)methyl)isoxazol-3-yl)(phenyl)methanone **(3l)**. White solid; 170 mg (93%), R_f = 0.42 (20% Ethylacetate : n-Hexane); Mp 136-138 °C; FT-IR (neat): υ = 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32-8.24 (m, 4H), 7.69-7.65 (m, 1H), 7.56-7.52 (m, 2H), 7.10-7.06 (m, 2H), 6.94 (s, 1H), 5.35 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.1, 167.2, 162.3, 162.0, 142.5, 135.4, 134.3, 130.7, 128.7, 126.1, 114.8, 105.0, 61.2; HRMS (EI-Quadrupole): *m/z* = 324.0748, calcd. for $C_{17}H_{12}N_2O_5$ (M^+): 324.0746.

4-((3-Benzoylisoxazol-5-yl)methoxy)benzonitrile **(3m)**. White solid; Mp 118-120 °C; 185 mg (96%), R_f = 0.44 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31-8.29 (m, 2H), 7.68-7.62 (m, 3H), 7.55-7.51 (m, 2H), 7.08-7.04 (m, 2H), 6.91 (s, 1H), 5.30 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.1, 167.4, 161.9, 160.7, 135.5, 134.3, 134.2, 130.7, 128.7, 118.7, 115.5, 105.6, 104.9, 60.9; HRMS (EI-Quadrupole): *m/z* = 304.0848, calcd. for $C_{18}H_{12}N_2O_3$ (M^+): 304.0848.

(5-((Naphthalen-2-yloxy)methyl)isoxazol-3-yl)(Phenyl)methanone **(3n)**.[75] White solid; 150 mg (91%), R_f = 0.59 (20% Ethylacetate : n-Hexane); Mp 111-113 °C (lit.[75] 110-111 °C); FT-IR (neat): υ = 1694, 1609, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31-8.29 (m, 2H), 7.80-7.74 (m, 3H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.53-7.44 (m, 3H), 7.40-7.38 (m, 1H), 7.25-7.20 (m, 2H), 6.92 (s, 1H), 5.35 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.4, 168.8, 161.9, 155.6, 135.6, 134.3, 134.1, 130.7, 129.9, 129.5, 128.6, 127.8, 126.9, 126.7, 124.3, 118.5, 107.4, 104.5, 61.1.

Phenyl (5-(m-tolyl)isoxazol-3-yl) methanone **(3o)**. White solid; 210 mg (93%), R_f = 0.80 (20% Ethylacetate : n-Hexane); Mp 84-86 °C; FT-IR (neat): υ = 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.36-8.33 (m, 2H), 7.67-7.63 (m, 3H), 7.55-7.52 (m, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.9, 171.0, 162.4, 138.9, 135.8, 134.0, 131.5, 130.7, 129.1, 128.6, 126.7, 126.6, 123.2, 100.1, 21.4; HRMS (EI-Quadrupole): *m/z* = 263.0946, calcd. for $C_{17}H_{13}NO_2$ (M^+): 263.0946.

Methyl 5-phenylisoxazole-3-carboxylate **(3p)**. White solid; 180mg (91%), R_f = 0.57 (20% Ethylacetate : n-Hexane); Mp 68-70 °C; FT-IR (neat): υ = 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74-7.72 (m, 2H), 7.42-7.40 (m, 3H), 6.86 (s, 1H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 160.5, 156.7, 130.9, 129.2, 126.6, 125.9, 99.9, 52.9; HRMS (EI-Quadrupole): *m/z* = 203.0582, calcd. for $C_{11}H_9NO_3$ (M^+): 203.0582.

Methyl 5-(m-tolyl)isoxazole-3-carboxylate **(3q)**. White solid; 175 mg (94%), R_f = 0.63 (20% Ethylacetate : n-Hexane); Mp 120-122 °C; FT-IR (neat): υ = 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55-7.52 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.22-7.19 (m, 1H), 6.83 (s, 1H), 3.93 (s, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 160.6, 156.7, 139.1, 131.7, 129.1, 126.6, 123.2, 99.9, 52.9, 21.5; HRMS (EI-Quadrupole): *m/z* = 217.0737, calcd. for $C_{12}H_{11}NO_3$ (M^+): 217.0739.

Methyl 5-((2,6-dichlorophenoxy)methyl)isoxazole-3-carboxylate **(3r)**. White solid; 135 mg (90%), R_f = 0.47 (20% Ethylacetate : n-Hexane); Mp 80-82 °C; FT-IR (neat): υ = 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.24 (m, 2H), 7.01-6.97 (m, 1H), 6.80 (s, 1H), 5.15 (s, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 160.3, 156.3, 150.3, 129.6, 129.3, 126.2, 104.9, 64.8, 53.0; HRMS (EI-Quadrupole): *m/z* = 300.9908, calcd. for $C_{12}H_9Cl_2NO_4$ (M^+): 300.9909.

Methyl 5-((perfluorophenoxy)methyl)isoxazole-3-carboxylate **(3s)**.White solid; 131 mg (90%), R_f = 0.52 (20% Ethylacetate : n-Hexane); Mp 60-62 °C; FT-IR (neat): υ = 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.76 (s, 1H), 5.24 (s, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 159.8, 156.4, 142.9, 140.6, 139.1, 136.7, 105.2, 66.1, 53.0; HRMS (EI-Quadrupole): *m/z* = 323.0217, calcd. for $C_{12}H_6F_5NO_4$ (M^+): 323.0217.

Methyl 5-((4-fluorophenoxy)methyl)isoxazole-3-carboxylate **(3t)**. White solid; 153 mg (91%), R_f = 0.39 (20% Ethylacetate : n-Hexane); Mp 82-84 °C; FT-IR (neat): υ = 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.02-6.98 (m, 2H), 6.92-6.88 (m,

2H), 6.75 (s, 1H), 5.17 (s, 2H), 3.98 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 160.1, 158.0 (d, *J* = 238.8 Hz), 156.3, 153.6 (d, *J* = 2.2 Hz), 116.2 (d, *J* = 23.2 Hz), 116.1 (d, *J* = 8.1 Hz), 104.0, 61.8, 52.9; HRMS (EI-Quadrupole): *m/z* = 251.0592, calcd. for $C_{12}H_{10}FNO_4$ (M^+): 251.0594.

Ethyl 5-decylisoxazole-3-carboxylate **(3u)**. Clear oil; 312 mg (92%), R_f = 0.52 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1719, 1590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.33 (s, 1H), 4.37-4.35 (m, 2H), 2.73-2.70 (m, 2H), 1.66-1.61 (m, 3H), 1.35-1.32 (m, 4H), 1.25-1.18 (m, 12H), 0.82-0.79 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 175.7, 160.2, 156.3, 101.4, 61.9, 31.8, 29.5, 29.4, 29.3, 29.1, 28.9, 27.4, 26.7, 22.6, 14.1, 14.0; HRMS (EI-Quadrupole): *m/z* = 281.1989, calcd. for $C_{16}H_{27}NO_3$ (M^+): 281.1991.

Phenyl(5-(trimethylsilyl)isoxazol-3-yl)methanone **(3v).**[75] White solid; Mp 33-35 ºC (lit. 32-34 ºC); 145mg (71%), R_f = 0.88 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 3141, 2960, 1665, 1590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.31 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 6.97 (s, 1H), 0.41 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 186.4, 179.4, 160.4, 136.2, 134.0, 130.8, 128.6, 113.6, -1.82.

3-Benzoyl-N-methylisoxazole-5-carboxamide **(3w)**. White solid; Mp 142-144 ºC; 174 mg (63%), R_f = 0.43 (50% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1732, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.26 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.69-7.65 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.38 (s, 1H), 6.88 (br-s, 1H), 3.06 (d, *J* = 5.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 184.7, 164.0, 162.4, 155.9, 135.3, 134.4, 130.6, 128.7, 107.6, 26.4. HRMS (ESI-QTOF): *m/z* = 231.0757, calcd. for $C_{12}H_{10}N_2O_3$ $(M+H)^+$: 231.0770.

(5-(Hydroxymethyl)-isoxazol-3-yl)(phenyl)methanone **(3x)**.[75] Pale yellow oil; 145mg (68%), R_f = 0.34 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 3425, 1662, 1593 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.27 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.67-7.63 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.78 (s, 1H), 4.86 (s, 2H), 2.68 (br-s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 185.8, 172.3, 161.8, 135.6, 134.2, 130.7, 128.6, 102.9, 56.4.

(5-(1-Hydroxycyclohexyl)isoxazol-3-yl)(phenyl)methanone **(3y)**.[72] Pale yellow oil; 185 mg (84%), R_f = 0.56 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 3517, 2934, 2859, 1742, 1698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.29 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.66-7.63 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.71 (s, 1H), 2.13 (br-s, 1H), 2.03-2.00 (m, 2H), 1.95-1.94 (m, 2H), 1.79-1.77 (m, 1H), 1.63-1.59 (m, 2H), 1.41-1.39 (m, 1H), 1.26-1.25 (m, 1H), 0.99-0.87 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 185.9, 178.8, 161.7, 135.7, 134.0, 130.7, 128.6, 100.8, 70.4, 36.6, 29.7, 25.1, 21.6, 14.1.

Ethyl 5-phenyl-4,5-dihydroisoxazole-3-carboxylate **(5a).**[76] Clear oil; 125 mg (62%), R_f = 0.31 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1718, 1592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.39-7.32 (m, 5H), 5.78 (dd, *J* = 11.5 and 9.0 Hz, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.64 (dd, *J* = 18.0 and 11.5 Hz, 1H), 3.22 (dd, *J* = 18.0 and 9.0 Hz, 1H), 1.38 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 160.6, 151.2, 139.5, 128.9, 128.7, 125.9, 84.9, 62.2, 41.5, 14.1.

Methyl 5-phenyl-4,5-dihydroisoxazole-3-carboxylate **(5b).**[76] Clear oil; 130 mg (69%), R_f = 0.34 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ =; 1715, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.39-7.31 (m, 5H), 5.78 (dd, *J* = 11.5, 9.0 Hz, 1H), 3.89 (s, 3H), 3.64 (dd, *J* = 18.0, 11.5 Hz, 1H), 3.22 (dd, *J* = 18.0, 9.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 160.9, 150.9, 139.4, 128.9, 128.7, 125.8, 85.0, 52.8, 41.3.

3-Ethyl 5-methyl 4,5-dihydroisoxazole-3,5-dicarboxylate **(5c).**[77] Clear oil; 180 mg (77%), R_f = 0.30 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ =1724, 1719, 1591 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.22 (dd, *J* = 11.0, 8.0 Hz, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 3.52-3.49 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 169.4, 159.8, 151.1, 79.7, 62.4, 53.0, 37.6, 14.1.

Dimethyl 4,5-dihydroisoxazole-3,5-dicarboxylate **(5d).**[77] Clear oil; 170 mg (78%), R_f = 0.34 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ =1728, 1714, 1597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.22 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.53-3.49 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 169.3, 160.2, 150.9, 79.8, 79.8, 53.1, 53.0, 37.6.

Methyl 5-methyl-4,6-dioxo-4,5,6,6a-tetrahydro-3aH-pyrrolo[3,4-d]isoxazole-3-carboxylate **(5e).**[78] White solid; Mp 207-209 ºC (lit. 205-208 ºC); 95 mg (50%), R_f = 0.30 (50% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1726, 1698 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 5.68 (d, *J* = 9.5 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 3.84 (s, 3H), 2.87 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ (ppm) 172.3, 170.7, 159.2, 148.6, 83.5, 54.7, 53.4, 25.6.

Triethyl isoxazole-3,4,5-tricarboxylate **(7a).**[79] Yellow oil; 154 mg (45%), R_f = 0.42 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1741, 1735, 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.49-4.42 (m, 6H), 1.44-1.38 (m, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 159.8, 159.1, 157.9, 155.2, 154.3, 117.9, 63.2, 63.0, 62.8, 13.97, 13.95, 13.93.

4,5-Diethyl 3-methyl isoxazole-3,4,5-tricarboxylate **(7b).**[79] Yellow oil; 160 mg (49%), R_f = 0.41 (20% Ethylacetate : n-Hexane); FT-IR (neat): υ = 1741, 1736, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.49-4.43 (m, 4H), 4.01 (s, 3H), 1.43-1.38 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 159.7, 159.2, 158.4, 155.1, 154.1, 117.9, 63.2, 62.8, 53.5, 13.9.

Trimethyl isoxazole-3,4,5-tricarboxylate **(7c).**[79] Yellow solid; 170 mg (49%), R_f = 0.38 (20% Ethylacetate : n-Hexane); Mp 98-100 ºC; FT-IR (neat): υ = 1738, 1735, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.02 (s, 6H), 3.98 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl3): δ (ppm) 160.1, 159.1, 158.4, 155.5, 154.1, 117.8, 53.6, 53.54, 53.52.

3,4-Bis(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide **(3a′)**.[73] Yellow oil; FT-IR (neat): υ = 2987, 1748, 1626 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.43 (q, *J* = 7.0 Hz, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 156.7, 155.1, 148.4, 106.8, 63.7, 13.94, 13.90.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ^{1}H NMR, ^{13}C{^{1}H}NMR spectra of **3a-y**, **5a-e** and **7a-c**; X-Ray analysis of **3k**; CIF file of **3k.**

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Notes

The authors declare no competing financial interest.

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