RESEARCH ARTICLE doi.org/10.1002/adsc.202100730

Advanced Synthesis & Catalysis

Mechanochemistry Enabled Construction of Isoxazole Skeleton *via* CuO Nanoparticles Catalyzed Intermolecular Dehydrohalogenative Annulation

Murugan Vadivelu,[a] Sugirdha Sampath,[a, b] Kesavan Muthu,[c] Kesavan Karthikeyan,[a,*] and Chandrasekar Praveen[d,*]

[a] Department of Chemistry, B. S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai-600048, Tamil Nadu, India
phone: (+91)-9840422604
E-mail: karthiclri@gmail.com

[b] Department of Metallurgical & Materials Engineering, Indian Institute of Technology-Madras (IITM), Chennai-600036, Tamil Nadu, India

[c] Interdisplinary Institute of Indian System of Medicine (IIISM), SRM Institute of Science and Technology, Kattankulathur-603203, Chengalpattu District, Tamil Nadu, India

[d] Electrochemical Power Sources Division, Central Electrochemical Research Institute (CSIR Laboratory), Alagappapuram, Karaikudi-630003, Sivagangai District, Tamil Nadu, India
phone: (+91)-9677733808
E-mail: chandrasekar.praveen@gmail.com

Manuscript received: June 12, 2021; Revised manuscript received: August 25, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100730

Abstract: A dehydrohalogenative approach for isoxazole annulation by partnering β-vinyl halides and α-nitrocarbonyls under mechanochemical setting was accomplished. This chemistry is operative under the cooperative catalysis of cupric oxide nanoparticles (< 50 nm) and DABCO. The key beneficial aspects of this protocol include: (i) broad substrate scope, (ii) no vigorous work-up, (iii) short reaction time, (iv) solvent-free condition, (v) commercial viability of substrates/reagents (vi) good chemical yields and selectivity. The other merit of this chemistry is the ease with which CuO can be recuperated and reused after the reaction with not much drop in catalytic activity for six runs. With no confinement to β-vinyl halides, the validated condition is also open to alkynes for isoxazole preparation, thereby establishing the broader utility of the current methodology.

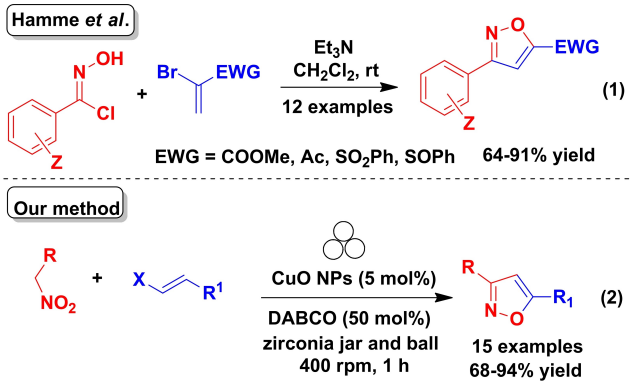
Keywords: Dehydrohalogenative annulation; CuO nanocatalysis; Mechanochemistry; Solvent-free conditions; Isoxazoles

Introduction

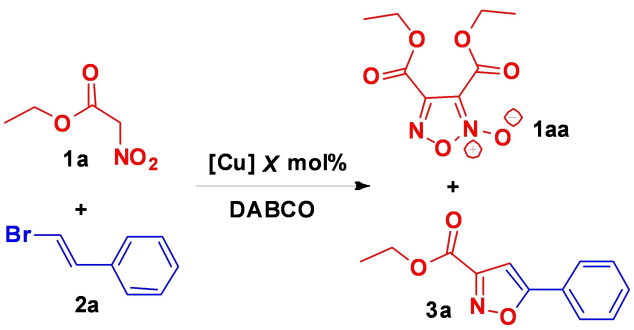
Within the regime of five-membered heterocycles, isoxazoles is one of the attractive ring systems which find wide applications ranging from medicinal chemistry to natural products to molecular devices.[1] Molecules possessing isoxazole cores emphasized its importance in the area of synthetic pharmaceuticals by exhibiting antiviral,[2,3] anti-inflamatory,[4,5] anticancer,[6] COX-2 inhibitory[7] and antinociceptive[8] potencies. Moreover, they are well recognized in synthetic chemistry as precursors/intermediates[9] and chiral ligands.[10] Their interesting liquid crystalline properties also opened new perspectives on isoxazole derivatives to meet optoelectronics application.[11] Hence, new strategic plans for constructing isoxazole skeleton is continuously emerging in recent times.[12] There are two major methodologies for isoxazole synthesis,[13] with the first one being the condensation between hydroxylamines and 1,3-dicarbonyls or their three-carbon 1,3-electrophilic variants (*viz.* α,β-enones, enamino ketones, β-alkylthioenones and ynones). The second one is the 1,3-dipolar cycloaddition between alkynes or olefins with *in situ* generated nitrile oxides from aldoximes or nitroalkanes.[14] Particularly, reaction between alkyne and a nitrile oxide component in a

[3+2] cycloaddition mode have received immense importance owing to its simplicity.[15–26] This particular chemistry can be operated in presence of CAN,[15] Boc_2O,[16] DMTMM,[17] DABCO[18] and TMEDA[19] under relatively mild conditions. Here, it is appropriate to mention that some approaches require stoichiometric proportion of strong base or acylating reagent to drive the dehydration step during the reaction course.[16,27] Also, high reaction temperature and compromise in regioselectivity are some of the associated shortcomings which need to be addressed. On the other hand, tedious preparative procedures for the requisite alkyne precursors also limit the scope towards substrate variation.

Taking the aforementioned issues into account and in conjunction with our ongoing interest on catalytic methods for heterocyclization,[28] we intend to develop a new strategy for isoxazole annulation by circumventing these limitations. At the outset, we turned our focus towards β-substituted vinyl halide as reaction partner instead of terminal alkyne. This is because of the extensive commercial viability coupled with step-economical synthesis of its derivatives compared to alkyne analogues.[29] Our literature perusal on this aspect revealed a base catalyzed 1,3-dipolar cycloaddition between α,α-disubstituted bromoalkenes and



Scheme 1. Literature precedence *vs* our approach for the dehydrohalaogenative isoxazole annulation.



Scheme 2. Optimization on prototype synthesis of **3 a**.[a]

α-chlorobenzaldoximes (Scheme 1, eq 1).[30] Prompted by this disclosure along with our search for milder conditions, we turned our attention to β-vinyl halides and α-nitrocarbonyl derivatives as reaction partners for isoxazole annulation (Scheme 1, eq 2).

This proposed chemistry worked well with the catalysis of cupric oxide nanoparticles (CuONPs) and DABCO under ball-milling conditions. With no confinement to β-vinyl halides, the scope of the methodology can be elaborated to terminal alkynes. This being said, that our methodology is applicable to both β-vinyl halides as well as terminal alkynes compared to some of the established procedures, wherein only terminal alkynes were shown to undergo isoxazole annulation with nitroesters (Table 1). Furthermore, wide substrate scope, solvent-free condition, catalyst recyclability as well as short reaction time are some of the beneficial features of this method and all these results are uncovered in this paper.

Results and Discussion

At the outset, we focused on the prototype reaction between ethyl nitroacetate (**1 a**) and β-bromostyrene (**2 a**) considering the following three points for validation (Scheme 2, Table 2). (i) Based on our previous knowledge in copper catalysis for

Table 1. Comparision of our methodology with selected prodecures for isoxazole synthesis *via* annulation of α-nitroesters.

Entry	Dipolarophile	Reaction conditions	[Ref.]
1	Terminal alkynes	DABCO (0.5 equiv), $CHCl_3$, 50 °C, 40 h	[19b]
2	Terminal alkynes	DABCO (0.1 equiv), $CHCl_3$, 60 °C, 80 h	[24]
3	Terminal alkynes	DABCO (0.5 equiv), H_2O, 60 °C, 18 h	[24]
4	Terminal alkynes	DABCO (0.1 equiv.)/$Cu(OAc)_2$ (0.05 equiv.), $CHCl_3$,60 °C, 23 h	[21]
5	Terminal alkynes	H_2O:PEG (1:1 v/v), 90 °C, 6 h	[43]
6	Terminal alkynes	Acetyl cholinechloride:urea (1:2), 100 °C, 4 h	[42]
7	Terminal alkynes	TEMPO (0.1 equiv.), open air, H_2O, 60 °C, 4 h	[28b]
8	β-Vinyl halides or Terminal alkynes	CuONPs (0.05 equiv.)/DABCO (0.5 equiv.), ball milling, ZrO_2, 400 rpm, 1 h	This work

Table 2. Screening results based on copper based catalysis for dehydrohalogenative annulation.

Entry	[Cu] (*X* mol%)	Time (h)	Yield **3 a** (%)[b]	Yield **4 a** (%)[b]
1	CuO (5)	12	22	trace
2	CuI (5)	12	5	trace
3	CuCl (5)	12	trace	–
4	$Cu(OAc)_2$ (5)	12	5	–
5	CuONP (5)	12	53	10
6	CuONP (1)	12	34	5
7[c]	CuONP (5)	3	68	5
8[c]	**CuONP (5)**	**1**	**82**	–
9[c,d]	CuONP (5)	1	55	–
10[c,e]	CuONP (5)	1	5	–
11[c,f]	–	1	10	–

[a] Reaction with **1 a** (1.5 mmol), **2 a** (1.0 mmol), DABCO (50 mol%) at 60 °C unless otherwise specified.
[b] Yield of isolated products after column chromatography.
[C] Ball-milling with ZrO_2 at 400 rpm.
[d] Reaction performed with 25 mol% of DABCO.
[e] Reaction performed in absence of DABCO.
[f] Reaction performed in absence of CuONP.

heterocyclization,[28a] we focused exclusively on copper based catalysts for optimization. (ii) Since solvent-free approach is one of our desired goals, only reaction under neat condition was planned. (iii) As the use of Lewis base could be essential, we preferred DABCO owing to its operational simplicity along with its proven ability to favor deprotonation of α-nitrocarbonyls to form nitrile oxides.[18] Thus, the use of 5 mol% of CuO at 60 °C affords the desired 3,5-disubstituted isoxazole (**3 a**) in 22% yield along with trace amount of 3,4-*bis*(ethoxycarbonyl)-1,2,5-oxadiazole 2-oxide (**1 aa**) as co-product after 12 h (entry 1). Though the yield is low, this preliminary result encouraged us to screen other copper sources such as CuI, CuCl and $Cu(OAc)_2$ with the overall results suggested that none of these copper sources turned out to be effective (entries 2–4). Up to this short screen, only the bulk form of CuO catalyzed the targeted reaction reasonably compared to other [Cu] catalysts (as per entry 1). This caught our attention and driven us to opt for CuO nanoparticles (CuONP), since it has high surface area/volume ratio to favor high chemical reactivity.[31] To this end, utilizing readily available CuONP (< 50 nm) increased the conversion to afford the product **3 a** in 53% together with co-product **1 aa** in 10% (entry 5). The better catalytic efficiency of CuONP than commercially viable bulk CuO can be reasoned to the larger surface area of CuONP (29 m^2/g) compared to bulk CuO (1.952 m^2/g).[32] A reduction in catalyst loading of CuONP (1 mol%) leads to a significant drop in the yield to 34% (entry 6). Since we already succeeded in triazole synthesis under mechanochemical conditions by DABCO / CuONP catalysis,[28a] we wonder if the yield of **3 a** could be further improved by taking advantage of ball-milling. To our delight, we observed a significant amelioration in yield of **3 a** to 68% along with a decrease of **1 aa** to 5% after milling in zirconia jar and ball at 400 rpm for 3 h (entry 7). As the yield enhanced with four-fold decrease in time, it points to the impact of mechanical force over conventional condition in driving the reaction.[33] Upon further decreasing the time to 1 h, yet another increment in yield to 82% was observed with complete absence of **1 aa** (entry 8). This observation suggests that prolonging the reaction time assists the formation of by-product **1 aa** in high proportions. Decreasing the stoichiometry of DABCO to 25 mol% led to a considerable decline in yield to 55% (entry 9). This is an indicative that DABCO might have taken the role of both Lewis base for deprotonating nitrile oxide as well as neutralizing the liberated HBr after the reaction. Needless to mention, a trial reaction devoid of either DABCO or CuONP generated the product in trace amount, thereby implying the complementary role of these species to effectuate the reaction (entries 10 and 11). Although milling balls of different density could be used for further optimization, we halted our optimization studies at this point in order to test the efficacy of the best condition obtained so far to other substrates (as per entry 8).

By following the optimized condition, substrate scope and generality of this chemistry was investigated with an array of α-nitroesters/carbonyls as well as β-bromostyrenes/olefins (Figure 1). The tested precursors underwent the reaction smoothly to provide 3,5-disubstituted isoxazole derivatives (**3 a**–**s**) in synthetically acceptable yields (68–92%). Initially, ethyl nitroacetate was allowed to react with substituted β-bromostyrenes possessing electronically different ring substituent like bromo, fluoro, methyl and alkoxy. Here, isoxazoles (**3 d**–**3 f**) derived from electron-rich alkynes were formed in slightly higher yields compared to those (**3 b** and **3 c**) obtained from electron-deficient halogen analogues. This is indication of the minor role of electronic effect in influencing the reactivity. Nevertheless, product like **3 b** possessing bromo tether could serve as synthetic handle as cross-coupling precursor for diverse organometallic transformations.[34] Apart from styrenes, the methodology can also be extended to 1-bromo-1-octene to afford the corresponding isoxazole (**3 g**) in 84% yield revealing that vinyl substrate is not a serious limitation for this process. Quite similar to ethyl esters, the methyl counterparts also participated in the reaction with equal aplomb to lend isoxazoles (**3 h**–**3 j**) in good chemical yields. However, the hydroxyl group tethered isoxazole (**3 k**) was isolated in a relatively low yield. Nevertheless, no side-product *via* oxidative dehydrogenation as documented by CuONP catalysis[35] was observed in the present case is confirmative of the

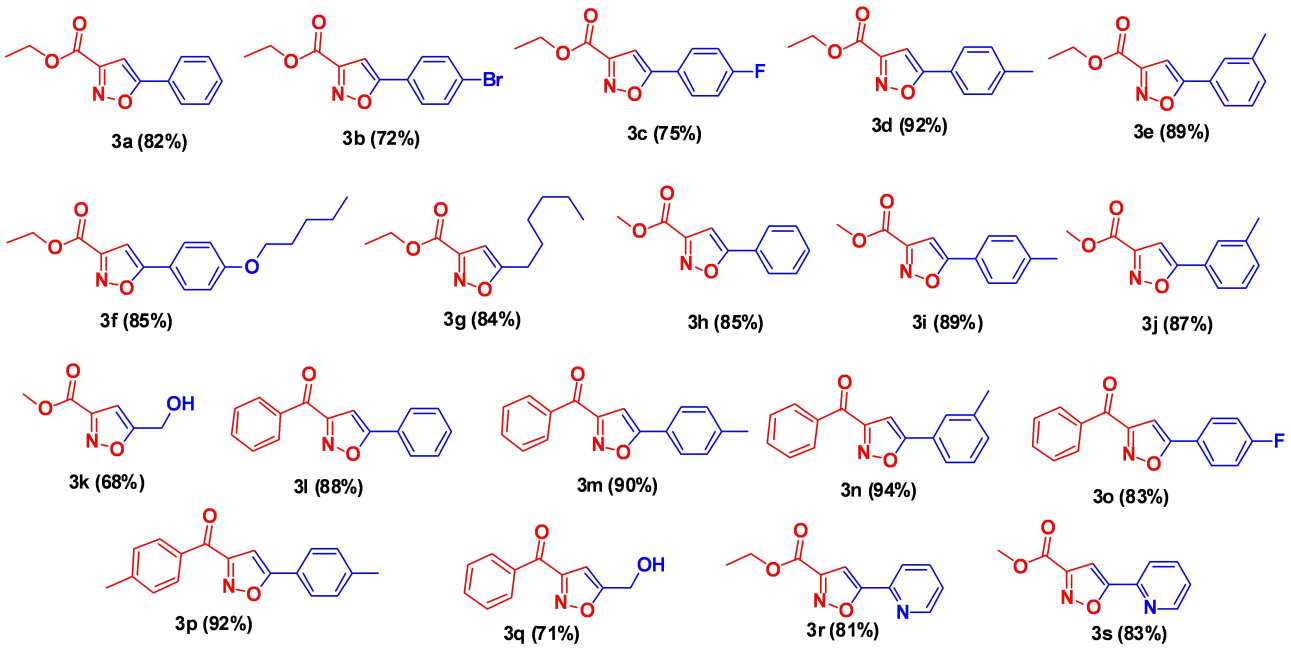
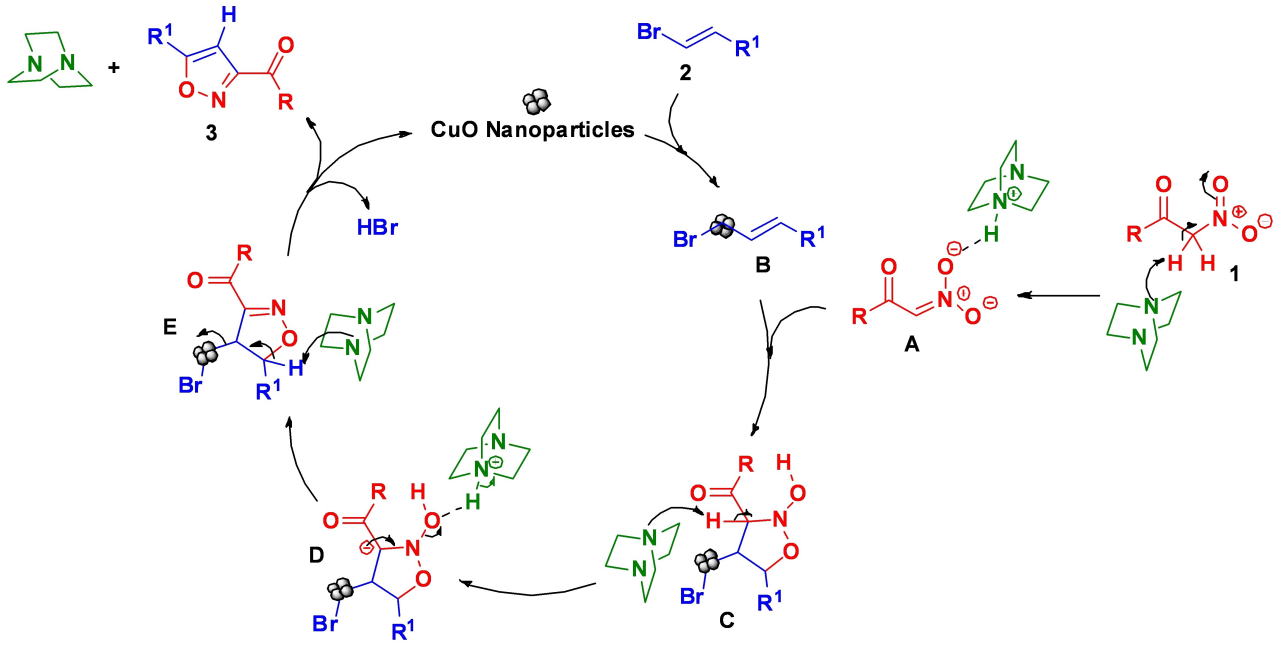


Figure 1. CuONP catalyzed mechanosynthesis of isoxazoles *via* dehydrohalogenative annulation approach.

hydroxyl group tolerance under our condition. Replacing α-ester by benzoyl group results in even better conversion of starting materials and chemical yields. This could be reasoned to the higher deprotonating ability of active methylene group in α-ketonitromethanes over α-nitroesters. Among this substrate class, the electron-rich methyl group lend products (**3 m**, **3 n** and **3 p**) in somewhat increased yield over electron with-drawing fluoro substituent (**3 o**). Within this substrate class, we also succeeded in preparing 5-(hydroxymethyl)-3-benzoylisoxazole (**3 q**), a pivotal intermediate for many therapeutic agents.[36a] As 2-pyridyl substituent attached to the C5-position of isoxazole ring is a key intermediate for several pharmacologically important receptors,[36b,c] we also elaborated our chemistry to obtain **3 r** and **3 s** in good yields. In place of α-nitrocarbonyls, we also checked the fate of $MeNO_2$ under the validated conditions in a reaction with **2 a**. However, the reaction turned out to be a complete failure attributing to the poor acidity of methyl hydrogen.

All the synthesized compounds were completely characterized by standard spectroscopic techniques like IR, ^1H, ^{13}C NMR and MS. As an illustrative example, the FT-IR spectrum of **3 c** displayed vibration peaks at 1728 and 1619 cm^{-1} corresponding to the stretching of C=O of ester and C=N of isoxazole ring respectively. ^1H NMR spectrum recorded in $CDCl_3$ showed a triplet at 1.45 ppm ($J = 7.0$ Hz, 3H) and a quartet at 4.48 ppm ($J = 7.0$ Hz, 2H). The chemical shift and splitting pattern agrees to the protons of $–OCH_2–$ and $–CH_3$ of ethyl ester group. Furthermore, the appearance of a singlet at 6.89 ppm is characteristic of C4-H proton of the isoxazolyl ring. ^{13}C NMR displayed peaks at δ 157.0, 99.7, 159.9 and 170.7 ppm were assigned to ester carbonyl carbon, *C*4-, *C*3- and *C*5- carbon of isoxazole ring respectively. Finally, mass spectra exhibited a molecular ion peak $[M]^+$ at *m/z* (obs.) = 235.0643, which is in good agreement with the theoretical value of *m/z* (expd.) = 235.0645. Based on the obtained results, a plausible mechanism was proposed to explain the probable sequence of events (Scheme 3). According to which, the reaction commences with the DABCO promoted deprotonation of α-nitroacetate/ketone **1** forming hydrogen bonded azinate intermediate **A**.[18,37] On the other hand, β-vinyl halide **2** interacts on the catalytic surface of CuONP to form transient species **B**. The later upon cycloaddition with azinate **A** generates the cyclic intermediate **C**. Subsequent abstraction of α-hydrogen by base leads to carbanion intermediate **D** appropriate to generate isoxazoline **E**. A second deprotonation by DABCO at *C*5-position of **E** effects dehydrobromination to afford the product **3** along with the regeneration of CuONP.

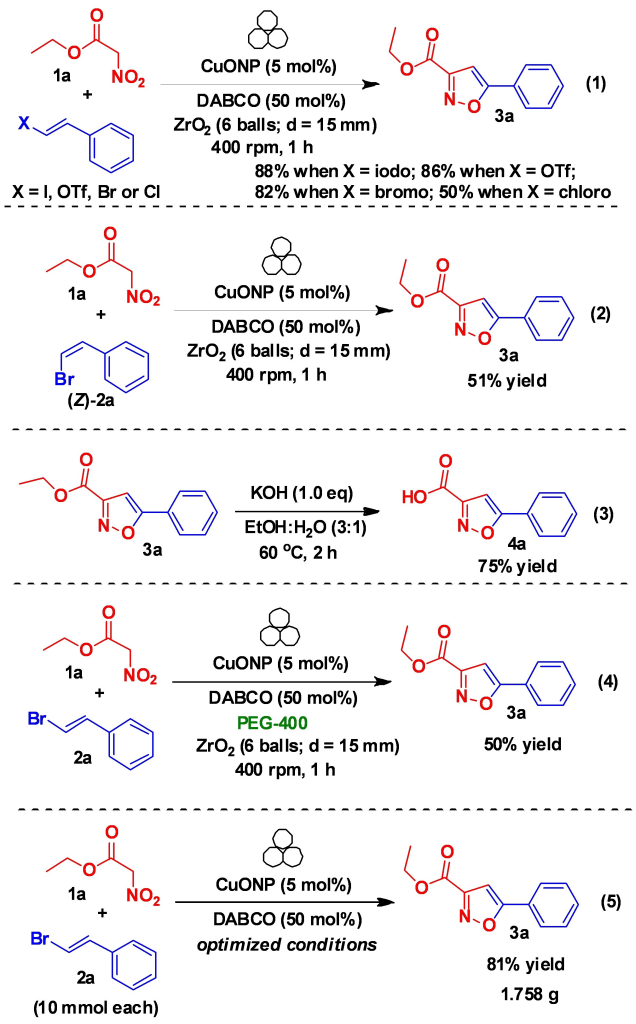
Not only limited to β-bromostyrenes, our chemistry can also be extended to other halogen (chloro and iodo) and pseudohalogen (OTf) partners (Scheme 4, eq 1). Under optimized condition, the yield of **3 a** gradually increased from chloro (50%) to bromo (82%) to triflate (86%) to iodo (88%), which is consistent with the leaving group ability in the order of I > OTf > Br > Cl. Though the iodo and triflate precursor produced equally good or a little higher yield over its bromo counterpart, the later offers the



Scheme 3. Tentative mechanistic picture of CuONP catalyzed isoxazole annulation.

advantage of simple preparation of its derivatives. Since, avoiding high production costs is one of the criteria of green engineering;[38] we believe β-bromostyrenes are better candidates compared to iodo and triflate counterparts. Likewise, *cis*-bromostyrene **(*Z*)-2 a** also underwent the dehydrobrominative annulation albeit generating **3 a** in a moderate 51% yield (Scheme 4, eq 2). This points to the fact that *trans*-isomer **2 a** involve in faster kinetics than the *cis*-isomer **(*Z*)-2 a** under the conditions. Keeping in mind the application of 3,5-disubstituted isoxazole-carboxylic acids as photosensitizer in DSSCs,[39] ester hydrolysis of 5-phenylisoxazole-3-carboxylate **3 a** was performed under basic condition to prepare 5-phenylisoxazole-3-carboxylic acid **4 a** in 75% yield (Scheme 4, eq 3). Though our mechanochemical approach worked effectively without requiring any petrochemical derived solvents, we also wanted to test its scope in biomass derived solvents to have one more green chemistry advantage. Hence, PEG-400 was included to the optimized reaction which produced 50% yield of **3 a** (Scheme 4, eq 4). Despite the relatively low yield in PEG-400, it is a sign of applicability of our chemistry in bio-solvents. Having succeeded in our objectives, we next sought out the possiblity of recuperation and recycling of CuONP. In this connection, a gram-scale synthesis of **3 a** using ethyl nitroacetate **1 a** (15.0 mmol, 1.99 g), β-bromostyrene **2 a** (10.0 mmol, 1.81 g), DABCO (5 mmol, 0.56 g) and CuONP (5 mol%, 39.46 mg) was performed (Scheme 4, eq 5). After completion of the reaction, the spent catalyst was removed by simple centrifugation, washed sequentially with few portions of water (5 mL), ethanol (5 mL) and acetone (5 mL) followed by drying at 110 °C for 2 h. The catalytic efficiency of the recovered CuONP was assessed for the first six cycles using fresh starting materials (**1 a** and **2 a**) for each cycle.

As clustered in Figure 2a, a slight diminution in product yield (82% to 76%) after each reuse of catalyst was observed. This diminution in yield of the product correlates well with the lower mass recovery of catalyst after each recycling step (Figure 2b). The minimal loss in mass also suggests the possibility of structural alteration of the catalyst after each recovery step. Therefore, SEM images were captured for the recovered catalyst after six runs and compared with commercial CuONP (Figure 3). Thus, the spent catalyst showed an agglomerated structure with reduced holes compared to the commercial sample which displayed a flaky aggregated morphology. Also, this difference in surface morphology which in turn led to different active sites of the catalyst cannot be precluded as a reason for the reduction in yield. However, it is unclear that the change in morphology occurs during the recycling course or at the ball-milling process. In order to get insight on kinetic profile, the reaction between **1 a** and **2 a** was performed at six different duration (10 to 60 min) and the conversion was monitored by crude NMR analysis. With respect to time, the concentration of **3 a** increases and **2 a** decreases respectively with 50% conversion reaching at 23 min (Figure 4a). Quite similar to conversion, the isolated yield of **3 a** also increases gradually with increase in time (Figure 4b). Since the



Scheme 4. Reactivity towards other β-halostyrenes (eq 1); *cis*-isomer (eq 2); ester hydrolysis of **3 a** (eq 3); reaction in PEG-400 (eq 4) and application in gram-scale synthesis of **3 a** (eq 5).

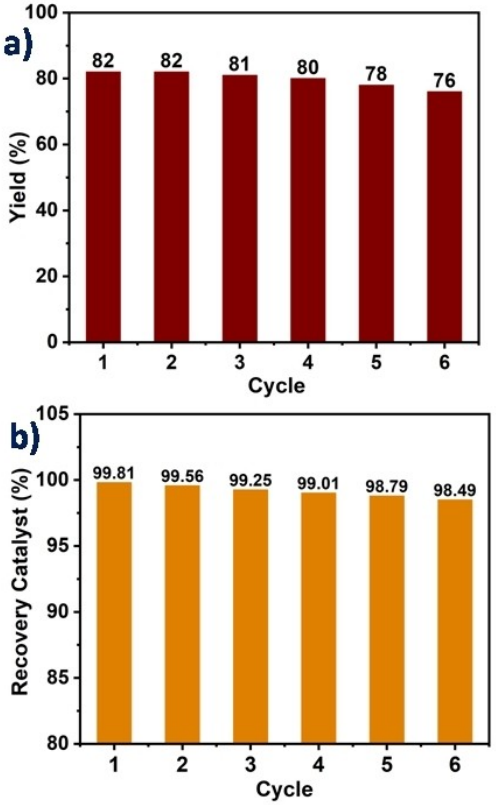


Figure 2. a) Yield of product **3 a** and b) recovered CuONP for the first six catalytic runs.

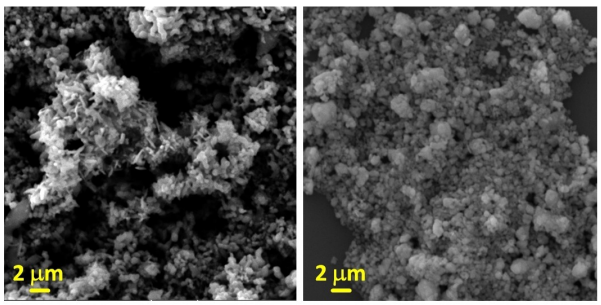


Figure 3. SEM images of commercial CuO nanoparticles (left) and spent catalyst after six cycles (right).

yield of **3 a** obtained in 1.0 mmol and 10.0 mmol scales (Scheme 4, eq 5) is identical, the reaction seems to follow zero order kinetics.

On the background of our previous success in TEMPO catalyzed Machetti–De Sarlo reaction for isoxazole synthesis,[28b] we became curious to expand the scope of present methodology to alkynes. Since our real focus was to strategize dehydrohalogenative annulation using β-halostyrenes, we screened only selected terminal alkynes **5 a-e** as reaction partners for α-nitroethylacetate **1 a** (Scheme 5, eq 1). It is gratifying to witness that under identical conditions, the tested alkynes produced the desired isoxazoles **6 a–e** in synthetically acceptable yields. Indeed, this is an added advantage of our protocol to accommodate not only β-halostyrenes but also terminal alkynes. The other beneficial aspect of the current approach is the chemoselectivity of alkynes towards cyclocondensation without undergoing oxidative homo-coupling known for terminal alkynes under copper catalysis.[40] Apparently, the reaction functioned well for acetylenes possessing long alkyl chain as well as electron-deficient *p*-NO_2-propargyloxy tether to lend the corresponding products (**6 a** and **6 b**) in excellent yields. Electron-rich naphyloxy alkyne also produced the respective isoxazole derivative (**6 c**) in synthetically acceptable yield. The chemistry is also amenable to short-chain alkynes containing cumbersome, yet synthetically valuable –(CO)NHMe and $–SiMe_3$ functionalities to afford

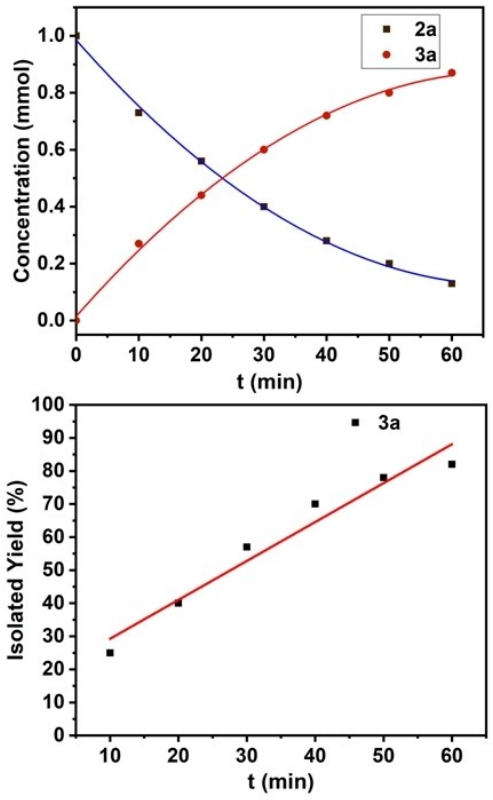
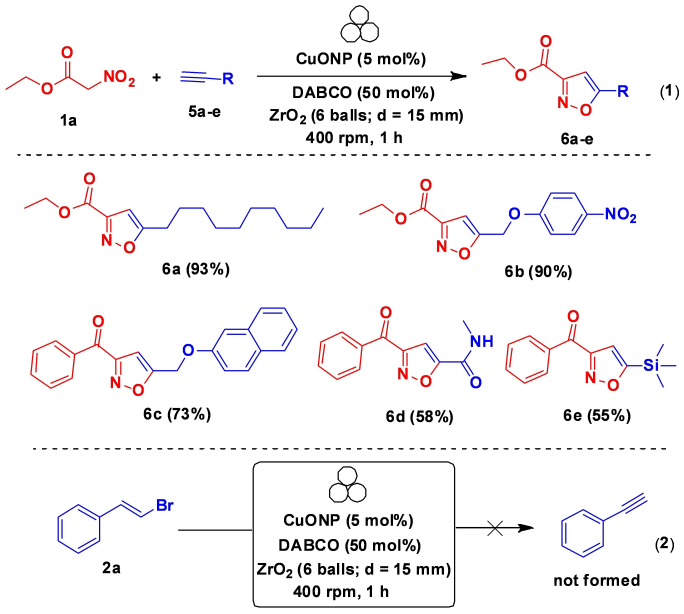


Figure 4. Kinetic plot showing the change in concentration of **2 a** and **3 a** (top) and yield profile of **3 a** at various reaction time (bottom).



Scheme 5. Synthetic extension to terminal alkynes (eq 1) and control reaction with β-bromostyrene (eq 2).

isoxazoles **6 d** and **6 e** in moderate yields. Since all alkynes generated 3,5-disubstituted isoxazoles exclusively without forming competitive 3,4-disubstituted isomers, it authenticates the regioselectivity of the overall process. In fact, the similar working pattern of terminal alkynes under the conditions originally developed for β-bromostyrenes raises doubt about the possibility of *in situ* elimination of β-bromostyrene to alkyne. Hence, a trial reaction under standardized mechanochemical condition comprising only β-bromostyrene **2 a** together with [Cu]/DABCO catalysts was carried out (Scheme 5, eq 2). The no formation of phenylacetylene with almost quantitative recovery of β-bromostyrene ruled out the possibility of *in situ* HBr elimination.[41] This observation in turn suggests that the dehydrobromination occurs only after the nitrile oxide cycloaddition step (as **C**, **D**, **E** in Scheme 3) and not possible during the initial step of catalyst interaction with β-bromostyrene (as **A** in Scheme 3).

Conclusion

In conclusion, we have successfully demonstrated a new synthetic approach for isoxazole ring formation under mechanochemical conditions. The reaction operates by partnering β-vinyl halides and α-nitrocarbonyls in an event of dehydrohalogenative annulation *via* combined catalysis of CuO nanoparticles and DABCO. With no restriction to β-vinyl halides, terminal alkynes also can be included in this chemistry to accomplish 3,5-disubstituted isoxazoles. The salient features of this methodology is solvent-free conditions, broad substrate scope, short reaction time, commercially viable starting materials, no vigorous solvent extraction, functional group tolerance, no co-product, chemo- and regioselectivity which are highly appealing from a sustainable chemistry perspective. Thanks to the presence of ester functionality in the final product, it can be subjected to final stage hydrolysis to prepare the corresponding carboxylic acid. On the other hand, our chemistry allowed the opportunity to recover and reuse CuONP for six catalytic cycles with not much change in the yield of the product as well as that of catalyst. Control experiments precluded the possibility of *in situ* dehydrobromination of β-vinyl halide to alkyne and confirmed that this step occurs at the late stage of catalytic cycle. Currently, we are exploring the scope of our chemistry to the synthesis of isoxazole based clinical drugs and will be reported shortly.

Experimental Section

General procedure for the preparation of 3,5-disubstituted isoxazoles (3)

A mixture of nitro compound **1** (1.5 mmol), bromoalkene **2** (1.0 mmol), DABCO (50 mol%) and CuO Nanoparticles

(5 mol%) were taken in a zirconia grinding jar (45 mL). To this mixture was added six zirconia balls ($d=15$ mm) and ball-milled for 1 h at 400 rpm. After completion of the reaction as indicated by TLC, 10 mL of ethyl acetate was added in portions to the residue and centrifuged to remove CuONP. The filtered organic solution was evaporated under reduced pressure and the resulting crude product was purified by silica gel (100–200 mesh) column chromatography using hexane/EtOAc to obtain the purified product **3**.

Ethyl 5-phenylisoxazole-3-carboxylate (3 a)[19b]

White solid; Yield: 178 mg (82%); mp: 47–49 °C; FT-IR (neat): $\upsilon=1726$, 1613, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.83-7.81 (m, 2H), 7.50-7.49 (m, 3H), 6.94 (s, 1H), 4.49 (q, $J=7.0$ Hz, 2H), 1.46 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.7, 160.0, 156.9, 130.8, 129.2, 126.6, 125.9, 99.9, 62.2, 14.2.

Ethyl 5-(4-bromophenyl)isoxazole-3-carboxylate (3 b)[12g]

White solid; Yield:213 mg(72%); mp:82–84 °C; FT-IR (neat): $\upsilon=1732$, 1618, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.61 (d, $J=8.5$ Hz, 2H), 7.57 (d, $J=8.5$ Hz, 2H), 6.86 (s, 1H), 4.41 (q, $J=7.0$ Hz, 2H), 1.37 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 170.6, 159.9, 157.1, 132.5, 127.4, 125.5, 125.3, 100.3, 62.3, 14.2.

Ethyl 5-(4-fluorophenyl)isoxazole-3-carboxylate (3 c)[12c]

White solid; Yield: 176 mg(75%); mp:68–70 °C; FT-IR (neat): $\upsilon=1728$, 1619, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.83-7.80 (m, 2H), 7.20 (t, $J=8.5$ Hz, 2H), 6.89 (s, 1H), 4.48 (q, $J=7.0$ Hz, 2H), 1.45 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 170.7, 164.1 (d, $J=250.8$ Hz), 159.9, 157.0, 128.1 (d, $J=8.6$ Hz), 123.0 (d, $J=3.4$ Hz), 116.4 (d, $J=22.1$ Hz), 99.7, 62.3, 14.2.

Ethyl 5-(*p*–tolyl)isoxazole-3-carboxylate (3 d)[12c]

White solid; Yield: 213 mg (92%); mp:58–60 °C; FT-IR (neat): $\upsilon=1725$, 1615, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.71 (d, $J=8.0$ Hz, 2H), 7.29 (d, $J=8.5$ Hz, 2H), 6.88 (s, 1H), 4.48 (q, $J=7.0$ Hz, 2H), 2.42 (s, 3H), 1.45 (t, $J=7.5$ Hz, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ (ppm) 171.9, 160.1, 156.9, 141.2, 129.8, 125.9, 123.9, 99.3, 62.2, 21.5, 14.2.

Ethyl 5-(*m*–tolyl)isoxazole-3-carboxylate (3 e)[42]

White solid; Yield: 206 mg (89%); mp:55–57 °C; FT-IR (neat): $\upsilon=1746$, 1619, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.65-7.62 (m, 2H), 7.40 (t, $J=7.5$ Hz, 1H), 7.31 (d, $J=7.5$ Hz, 1H), 6.93 (s, 1H), 4.50 (q, $J=7.5$ Hz, 2H), 2.45 (s, 3H), 1.47 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.9, 160.1, 156.9, 139.0, 131.6, 129.1, 126.6, 126.5, 123.1, 99.8, 62.2, 21.4, 14.2.

Ethyl 5-(4-(pentyloxy)phenyl)isoxazole-3-carboxylate (3 f)[43]

White solid; Yield: 258 mg (85%); mp:70–72 °C; FT-IR (neat): $\upsilon=1726$, 1625, 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.64 (d, $J=8.5$ Hz, 2H), 6.89 (d, $J=8.5$ Hz, 2H), 6.70 (s, 1H), 4.38 (q, $J=7.0$ Hz, 2H), 3.92 (t, $J=6.5$ Hz, 2H), 1.75-1.69 (m, 2H), 1.40-1.30 (m, 7H), 0.86 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.8, 161.2, 160.2, 156.9, 127.5, 119.2, 115.0, 98.4, 68.2, 62.1, 28.8, 28.1, 22.4, 14.2, 13.9.

Ethyl 5-hexylisoxazole-3-carboxylate (3 g)[12g]

Clear oil; Yield: 189 mg (84%); FT-IR (neat): $\upsilon=1716$, 1597, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.33 (s, 1H), 4.36 (q, $J=7.5$ Hz, 2H), 2.72 (t, $J=7.5$ Hz, 2H), 1.66 (q, $J=7.0$ Hz, 2H), 1.34 (t, $J=7.5$ Hz, 3H), 1.30–1.28 (m, 2H), 1.25–1.22 (m, 4H), 0.82-0.80 (m, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ (ppm) 175.7, 160.3, 156.3, 101.4, 62.0, 31.3, 28.6, 27.3, 26.7, 22.4, 14.1, 13.9.

Methyl 5-phenylisoxazole-3-carboxylate (3 h)[44]

White solid; Yield: 173 mg(85%); mp65–67 °C; FT-IR (neat): $\upsilon=1722$, 1648, 1235 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.74–7.72 (m, 2H), 7.41–7.40 (m, 3H), 6.86 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.8, 160.5, 156.7, 130.9, 129.2, 126.6, 125.9, 99.9, 52.9.

Methyl 5-(*p*-tolyl)isoxazole-3-carboxylate (3 i)[44]

White solid; Yield: 193 mg(89%); mp128–130 °C; FT-IR (neat): $\upsilon=1728$, 1642, 1226 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.70 (d, $J=8.0$ Hz, 2H), 7.29 (d, $J=8.5$ Hz, 2H), 6.88 (s, 1H), 4.01 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 172.0, 160.5, 156.6, 141.3, 129.8, 125.9, 123.9, 99.3, 52.9, 21.5.

Methyl 5-(*m*-tolyl)isoxazole-3-carboxylate (3 j)[28b]

White solid; Yield: 189 mg(87%);mp:118–121 °C; FT-IR (neat): $\upsilon=1726$, 1642, 1224 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.54–7.51 (m, 2H), 7.29 (t, $J=7.5$ Hz, 1H), 7.21–7.19 (m, 1H), 6.83 (s, 1H), 3.92 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 172.0, 160.5, 156.6, 139.0, 131.7, 129.1, 126.5, 123.1, 99.8, 52.9, 21.4.

Methyl 5-(hydroxymethyl)isoxazole-3-carboxylate (3 k)[45]

Colourless oil; Yield: 107 mg (68%); FT-IR (neat): $\upsilon=3341$, 1726, 1642, 1224 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.67 (s, 1H), 4.82 (s, 2H), 3.97 (s, 3H), 3.57 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 173.8, 160.3, 155.9, 102.5, 56.1, 53.0.

Phenyl (5-phenylisoxazol-3-yl)methanone (3 l)[43]

White solid; Yield: 219 mg (88%); mp:78–80 °C; FT-IR (neat): $\upsilon=1665$, 1628, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ

(ppm) 8.26 (d, J=8.5 Hz, 2H), 7.76 (d, J=7.5 Hz, 2H), 7.57 (t, J=7.5 Hz, 1H), 7.46-7.40 (m, 5H), 6.96 (s, 1H); ^{13}C NMR (125 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.

Phenyl (5-(*p*-tolyl)isoxazol-3-yl)methanone (3 m)[43]

White solid; Yield: 236 mg(90%); mp:118–120 °C; FT-IR (neat): υ = 1664, 1624, 1223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.37 (d, J=8.0 Hz, 2H), 7.76 (d, J=8.0 Hz, 2H), 7.68 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 7.02 (s, 1H), 2.44 (s, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ (ppm) 185.9, 170.9, 162.4, 141.2, 135.8, 134.0, 130.7, 129.9, 128.6, 125.9, 124.0, 99.7, 21.6.

Phenyl-(5-(*m*-tolyl)isoxazol-3-yl)methanone (3 n)[28b]

White solid; Yield: 247 mg (94%); mp:85–87 °C; FT-IR (neat): υ = 1645, 1628, 1213 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.26 (d, J=7.5 Hz, 2H), 7.57 (d, J=8.0 Hz, 3H), 7.46 (t, J= 7.5 Hz, 2H), 7.31 (t, J=7.5 Hz, 1H), 7.21 (d, J=7.5 Hz, 1H), 6.95 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 185.9, 171.0, 162.4, 138.9, 135.8, 134.1, 131.6, 130.7, 129.1, 128.6, 126.6, 126.5, 123.2, 100.2, 21.5.

(5-(4-Fluorophenyl)isoxazol-3-yl)(phenyl) methanone (3 o)[46]

White solid; Yield: 222 (83%); mp:144–146 °C; FT-IR (neat): υ = 1668, 1625, 1231 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.25 (d, J=8.0 Hz, 2H), 7.77–7.74 (m, 2H), 7.58 (t, J= 7.5 Hz, 1H), 7.45 (t, J=8.0 Hz, 2H), 7.11 (t, J=8.5 Hz, 2H), 6.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 185.7, 169.8, 164.1 (d, J=250.6 Hz), 162.5, 135.7, 134.1, 130.7, 128.6, 128.1 (d, J=8.5 Hz), 123.1 (d, J=3.3 Hz), 116.4 (d, J= 22.0 Hz), 100.1.

p-Tolyl(5-(*p*-tolyl)isoxazol-3-yl)methanone (3 p)[49]

White solid; Yield: 255 mg (92%); mp:108–110 °C; FT-IR (neat): υ = 1674, 1610, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.26 (d, J=8.0 Hz, 2H), 7.74 (d, J=8.0 Hz, 2H), 7.34-7.29 (m, 4H), 6.97 (s, 1H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 185.5, 170.9, 162.6, 145.2, 141.1, 133.3, 130.9, 129.8, 129.3, 125.9, 124.1, 99.7, 21.8, 21.6.

(5-(Hydroxymethyl)-isoxazol-3-yl)(phenyl) methanone (3 q)[48]

Pale yellow oil; Yield:144 mg (71%), FT-IR (neat): υ = 3435, 1661, 1573 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.28 (dd, J=8.5, 1.5 Hz, 2H), 7.66 (t, J=7.5 Hz, 1H), 7.53 (t, J= 8.0 Hz, 2H), 6.78 (s, 1H), 4.87 (s, 2H), 2.69 (br-s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 185.8, 172.3, 161.8, 135.6, 134.2, 130.7, 128.7, 102.9, 56.4.

Ethyl 5-(pyridin-2-yl)isoxazole-3-carboxylate (3 r)[50]

Yellow solid; Yield: 177 mg (81%); mp: 64–66 °C; FT-IR (neat): υ = 1720, 1618, 1241 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.64 (d, J=4.5 Hz, 1H), 7.87 (d, J=7.5 Hz, 1H), 7.78 (t, J=8.0 Hz, 1H), 7.32-7.29 (m, 1H), 7.23 (s, 1H), 4.40 (q, J= 7.5 Hz, 2H), 1.36 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 170.9, 159.7, 157.2, 150.2, 145.7, 137.2, 124.9, 121.1, 102.7, 62.3, 14.1.

Methyl 5-(pyridin-2-yl)isoxazole-3-carboxylate (3 s)

Yellow solid; Yield: 169 mg (83%); mp: 72–74 °C; FT-IR (neat): υ = 1716, 1632, 1255 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.72 (d, J=4.5 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.86 (dt, J=8.0, 1.5 Hz, 1H), 7.40-7.37 (m, 1H), 7.31 (s, 1H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.1, 160.2, 156.9, 150.3, 145.8, 137.2, 124.9, 121.1, 102.7, 52.9.

Experimental procedure for the preparation of 5-phenylisoxazole-3-carboxylic acid (4 a)

To a solution of ethyl 5-phenylisoxazole-3-carboxylate (**3 a**, 1.0 mmol) in EtOH/H_2O (3:1 v/v), was added KOH (1.0 mmol) and heated at 60 °C for 2 h. Upon completion of the reaction, as monitored by TLC, the reaction was quenched invariably by the addition of 10 ml of water. Unreacted ester, if any, was removed by diethylether extraction. The aqueous layer was acidified with 6 N HCl to reach pH = 2. The acid precipitated on standing, was filtered off and dried under vacuum to obtained 5-phenyl-isoxazole-3-carboxylic acid (**4 a**).

5-Phenylisoxazole-3-carboxylic acid (4 a)[47]

White solid; Yield: 142 mg (75%); mp: 158–160 °C; FT-IR (neat): υ = 3456, 1728, 1623, 1268 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.88–7.86 (m, 2H), 7.52–7.50 (m, 3H), 7.29 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 171.4, 161.2, 158.1, 131.4, 129.8, 126.5, 126.2, 101.0.

General procedure for the preparation of 3,5-disubstituted isoxazoles (6)

A mixture of nitro compound **1** (1.5 mmol), alkynes **5** (1.0 mmol), DABCO (50 mol%) and CuO nanoparticles (5 mol%) were taken in a zirconia grinding jar (45 mL). To this mixture was added six zirconia balls (d=15 mm) and ball-milled for 1 h at 400 rpm. After completion of the reaction as indicated by TLC, 10 mL of ethyl acetate was added in portions to the residue and centrifuged to remove CuONP. The filtered organic solution was evaporated under reduced pressure and the resulting crude product was purified by silica gel (100–200 mesh) column chromatography using hexane/EtOAc to obtain the purified product **6**.

Ethyl 5-decylisoxazole-3-carboxylate (6 a)[28b]

Clear oil; Yield: 262 mg (93%); FT-IR (neat): υ = 1721, 1594, 1224 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.33 (s, 1H), 4.36 (q, J=7.0 Hz, 2H), 2.72 (t, J=7.5 Hz, 2H), 1.64 (q, J=

7.5 Hz, 2H), 1.34 (t, J=7.0 Hz, 3H), 1.30-1.12 (s, 14H), 0.81 (t, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 175.7, 160.3, 156.3, 101.4, 62.0, 31.9, 29.5, 29.4, 29.3, 29.2, 28.9, 27.4, 26.7, 22.7, 14.1, 14.0.

Ethyl 5-((4-nitrophenoxy)methyl)isoxazole-3-carboxylate (6 b)[28b]

White solid; Yield: 263 mg (90%); mp: 126–128 °C; FT-IR (neat): υ=1752, 1638, 1468, 1425 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.27–8.24 (m, 2H), 7.09–7.05 (m, 2H), 6.83 (s, 1H), 5.34 (s, 2H), 4.47 (q, J=8.0 Hz, 2H), 1.44 (t, J=8.0 Hz, 3H); ^{13}C 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.

(5-((Naphthalen-2-yloxy)methyl)isoxazol-3-yl)(phenyl)methanone (6 c)[48]

White solid; Yield: 240 mg (73%); mp: 114–116 °C; FT-IR (neat): υ=1688, 1619, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31–8.29 (m, 2H), 7.80-7.74 (m, 3H), 7.65 (t, J=9.0 Hz, 1H), 7.54–7.44 (m, 3H), 7.40–7.36 (m, 1H), 7.25—7.21 (m, 2H), 6.93 (s, 1H), 5.36 (s, 2H); ^{13}C 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, 129.6, 128.6, 127.8, 126.9, 126.7, 124.3, 118.5, 107.4, 104.5, 61.1.

3-Benzoyl-N-methylisoxazole-5-carboxamide (6 d)[28b]

White solid; Yield: 133 mg (58%); mp: 142–144 °C; FT-IR (neat): υ=1742, 1628 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.27 (dd, J=8.5, 1.0 Hz, 2H), 7.69–7.66 (m, 1H), 7.54 (t, J=7.5 Hz, 2H), 7.38 (s, 1H), 6.89 (br-s, 1H), 3.07 (d, J=5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 184.7, 164.1, 162.4, 155.9, 135.3, 134.4, 130.6, 128.7, 107.6, 26.4.

Phenyl(5-(trimethylsilyl)isoxazol-3-yl)methanone (6 e)[48]

White solid; Yield: 135 mg (55%); mp: 34–36 °C; FT-IR (neat): υ=3151, 2969, 1665, 1592 cm^{-1}; ^{1}H 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), 7.53 (t, J=7.5 Hz, 2H), 6.98 (s, 1H), 0.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 186.4, 179.4, 160.4, 136.2, 134.1, 130.8, 128.7, 113.6, –1.81.

Experimental procedure for the preparation of 3 a in PEG-400 medium

A mixture of **1 a** (1.0 mmol), **2 a** (1 mmol), DABCO (50 mol%), CuO nanoparticles (5 mol%) and PEG-400 (2 mL) were taken in a zirconia grinding jar (45 mL). To this mixture was added six zirconia balls (d=15 mm) and ball-milled for 1 h at 400 rpm. Then, 10 mL of ethyl acetate was added in portions to the residue and filtered off the CuONP. The filtered organic solution was extracted with EtOAc/water (3×10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by silica gel (100-200 mesh) column chromatography using hexane/EtOAc to obtain the product **3 a** in 50% yield.

Experimental procedure for catalyst recycling

The recyclability of catalyst was performed during the gram-scale synthesis of **3 a**. After completion of the reaction as evidenced by TLC, the reaction mixture was treated with 5 mL of ethanol, centrifuged at 1000 rpm and filtered-off the catalyst on a membrane filter (0.2 μM). The obtained spent catalyst was washed sequentially with 5 mL each of water, ethanol and acetone followed by drying for 2 h at 110 °C. The catalyst recovered in this manner was reused for six subsequent cycles by employing fresh starting materials (**1 a** and **2 a**) for each cycle.

Acknowledgements

One of the authors, K. K. acknowledges the Tamil Nadu State Council for Science and Technology (TNSCST), India for financial support (TNSCST/STP-PRG/AR/2018-2019/9331). C. P. would like to thank the Council of Scientific and Industrial Research (CSIR) and Department of Science & Technology (DST) for Senior Research Associateship (13(9137-A)/2020-Pool)) and INSPIRE faculty research grant (IFA14-MS27) respectively. For providing Senior Research Fellowship (SRF), M. V. thanks the Council of Scientific and Industrial Research (CSIR), India. The communication number for this manuscript as assigned by the Ethics and Scientific Vigilance Committee of CSIR-CECRI is CECRI/PESVC/Pubs./2021-098.

References

[1] a) L. Carlsen, D. Dopp, H. Dopp, F. Duus, H. Hartman, S. Lang-Fugmann, B. Schulze, R. K. Smalley, B. J. Wakefield, In *Houben-Weyl Methods of Organic Chemistry*, Vol. E8a; E. Schaumann, Ed., Georg Thieme Verlag: Stuttgart, Germany, **1992**, 45–204; b) J. Sperry, D. Wright, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740; c) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.* **2005**, *9*, 925–958; d) V. Jager, P. A. Colinas, In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Padwa, A., Ed.; Wiley: Hoboken, **2002**, *59*, 361–472; e) R. Kakarla, J. Liu, D. Naduthambi, W. Chang, R. T. Mosley, D. Bao, H. M. M. Steuer, M. Keilman, S. Bansal, A. M. Lam, W. Seibel, S. Neilson, P. A. Furman, M. J. Sofia, *J. Med. Chem.* **2014**, *57*, 2136–2160; f) B. Holzer, B. Stöger, P. Kautny, G. Reider, C. Hametner, J. Fröhlich, D. Lumpi, *CrystEngComm.* **2018**, *20*, 12–16.

[2] Y.-S. Lee, B. H. Kim, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1395–1397.

[3] S. Srivastava, L. K. Bajpai, S. Batra, A. P. Bhaduri, J. P. Maikhuri, G. Gupta, J. D. Dhar, *Bioorg. Med. Chem.* **1999**, *7*, 2607–2613.

[4] G. Daidone, D. Raffa, B. Maggio, F. Plescia, V. M. C. Cutuli, N. G. Mangano, A. Caruso, *Arch. Pharm.* **1999**, *332*, 50–54.

[5] J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel, K. Seibert, *J. Med. Chem.* **2000**, *43*, 775–777.

[6] a) W.-T. Li, D.-R. Hwang, C.-P. Chen, C.-W. Shen, C.-L. Huang, T.-W. Chen, C.-H. Lin, Y.-L. Chang, Y.-Y. Chang, Y.-K. Lo, H.-Y. Tseng, C.-C. Lin, J.-S. Song, H.-C. Chen, S.-J. Chen, S.-H. Wu, C.-T. Chen, *J. Med. Chem.* **2003**, *46*, 1706–1715; b) G. C. Arya, K. Kaur, V. Jaitak, *Eur. J. Med. Chem.* **2021**, *221*, 113511.

[7] J. J. Talley, *Prog. Med. Chem.* **1999**, *36*, 201–234.

[8] M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, V. Dal Piaz, *J. Med. Chem.* **2003**, *46*, 1055–1059.

[9] a) A. K. Roy, B. Rajaraman, S. Batra, *Tetrahedron* **2004**, *60*, 2301–2310; b) K. S. Wankhede, V. V. Vaidya, P. S. Sarang, M. M. Salunkhe, G. K. Trivedi, *Tetrahedron Lett.* **2008**, *49*, 2069–2073; c) Y.-P. Han, X.-S. Li, Z. Sun, X.-Y. Zhu, M. Li, X.-R. Song, Y.-M. Liang, *Adv. Synth. Catal.* **2017**, *359*, 2735–2740; d) W. Yang, Y. Chen, Y. Yao, Q. Lin, D. Yang, *Adv. Synth. Catal.* **2019**, *17*, 5634–5642; e) S. Mukhopadhyay, D. S. Barek, I. Avasthi, S. Batra, *Adv. Synth. Catal.* **2017**, *359*, 4050–4056.

[10] a) F. M. Cordero, L. Lascialfari, F. Machetti, *Prog. Heterocycl. Chem.* **2021**, *32*, 365–395; b) K. Takenaka, S. Nakatsuka, T. Tsujihara, P. S. Koranne, H. Sasai, *Tetrahedron: Asymmetry* **2008**, *19*, 2492–2496.

[11] a) M. Tanaka, T. Haino, K. Ideta, K. Kubo, A. Mori, Y. Fukazawa, *Tetrahedron* **2007**, *63*, 652–665; b) A. A. Vieira, F. R. Bryk, G. Conte, A. J. Bortoluzzi, H. Gallardo, *Tetrahedron Lett.* **2009**, *50*, 905–908; c) L. D. Lopes, A. A. Merlo, *Mol. Cryst. Liq. Cryst.* **2015**, *612*, 149–157.

[12] a) J. Li, Z. Lin, W. Wu, H. Jiang, *Org. Chem. Front.* **2020**, *7*, 2325–2348; b) O. Bondarenko, N. V. Zyk, *Chem. Heterocycl. Compd.* **2020**, *56*, 694–707; c) Y. Ma, Y. Chen, C. Lou, Z. Li, *Asian J. Org. Chem.* **2020**, *9*, 1018–1021; d) L. Wang, Y. Tao, N. Zhang, S. Li, *Tetrahedron Lett.* **2021**, *64*, 152739; e) L. Li, S. Huang, K. Mao, L. Lv, Z. Li, *Tetrahedron Lett.* **2021**, *71*, 153052; f) J. Ge, Q. Ding, X. Long, X. Liu, Y. Peng, *J. Org. Chem.* **2020**, *85*, 13886–13894; g) X.-W. Zhang, X.-L. He, N. Yan, H.-X. Zheng, X.-G. Hu, *J. Org. Chem.* **2020**, *85*, 15726–15735; h) W. Wu, C. Li, F. Zhou, J. Li, X. Xu, H. Jiang, *Adv. Synth. Catal.* **2019**, *361*, 3813–3823; i) M. Fu, H. Li, M. Su, Z. Cao, Y. Liu, Q. Liu, C. Guo, *Adv. Synth. Catal.* **2019**, *361*, 3420–3429.

[13] a) F. Hu, M. Szostak, *Adv. Synth. Catal.* **2015**, *357*, 2583–2614; b) P. Margaretha, In *Sci. Synth.*; Thieme, **2010**; Vol. *1*, p 109.

[14] a) D. Giomi, F. M. Cordero, F. Machetti, In *Comprehensive Heterocyclic Chemistry III*, A. R. Katritzky, Ed., Elsevier, Oxford, U. K., **2008**, Vol. *4*, p 365–486; b) A. M. S. Silva, A. C. Tomé, T. M. V. D. Pinho e Melo, J. Elguero, In *Modern Heterocyclic Chemistry*, J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Eds., Wiley-VCH, Weinheim, Germany, **2011**, p 727–808.

[15] T. Sugiyama, *Appl. Chem.* **1995**, *9*, 399–411.

[16] Y. Basel, A. Hassner, *Synthesis* **1997**, *3*, 309–312.

[17] G. Giacomelli, L. De Luca, A. Porcheddu, *Tetrahedron* **2003**, *59*, 5437–5440.

[18] L. Cecchi, F. De Sarlo, F. Machetti, *Tetrahedron Lett.* **2005**, *46*, 7877–7879.

[19] a) L. Cecchi, F. De Sarlo, C. Faggi, F. Machetti, *Eur. J. Org. Chem.* **2006**, 3016–3020; b) L. Cecchi, F. De Sarlo, F. Machetti, *Eur. J. Org. Chem.* **2006**, 4852–4860.

[20] F. Machetti, L. Cecchi, E. Trogu, F. De Sarlo, *Eur. J. Org. Chem.* **2007**, 4352–4359.

[21] A. Baglieri, L. Meschisi, F. De Sarlo, F. Machetti, *Eur. J. Org. Chem.* **2016**, 4643–4655.

[22] J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 5491–5494; *Angew. Chem. Int. Ed.* **2011**, *50*, 5379–5382.

[23] K.-I. Itoh, T. Aoyama, H. Satoh, Y. Fujii, H. Sakamaki, T. Takido, *Tetrahedron Lett.* **2011**, *52*, 6892–6895.

[24] E. Trogu, C. Vinattieri, F. De Sarlo, F. Machetti, *Chem. Eur. J.* **2012**, *18*, 2081–2093.

[25] S. Mohammed, R. A. Vishwakarma, S. B. Bharate, *RSC Adv.* **2015**, *5*, 3470–3473.

[26] S. E. Denmark, J. M. Kallemeyn, *J. Org. Chem.* **2005**, *70*, 2839–2842.

[27] a) K. Harada, E. Kaji, S. Zen, *Chem. Pharm. Bull.* **1980**, *28*, 3296–3303; b) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Org. Lett.* **2003**, *5*, 391–394; c) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 3555–3558.

[28] a) M. Vadivelu, S. Sugirdha, P. Dheenkumar, Y. Arun, K. Karthikeyan, C. Praveen, *Green Chem.* **2017**, *19*, 3601–3610; b) M. Vadivelu, S. Sugirdha, K. Kesavan, K. Karthikeyan, C. Praveen, *J. Org. Chem.* **2019**, *84*, 13636–13645; c) M. Vadivelu, A. A. Raheem, S. Sugirdha, G. Bhaskar, K. Karthikeyan, C. Praveen, *Arkivoc* **2018**, *iii*, 90–101.

[29] J. Szyling, A. Franczyk, P. Pawluć, B. Marciniec, J. Walkowiak, *Org. Biomol. Chem.* **2017**, *15*, 3207–3215.

[30] S. Dadiboyena, J. Xu, A. T. Hamme, *Tetrahedron Lett.* **2007**, *48*, 1295–1298.

[31] N. Verma, N. Kumar, *ACS Biomater. Sci. Eng.* **2019**, *5*, 1170–1188.

[32] M. L. Kantam, J. Yadav, S. Laha, B. Sreedhar, S. Jha, *Adv. Synth. Catal.* **2007**, *349*, 1938–1942.

[33] a) T. Friščic, C. Mottillo, H. M. Titi, *Angew. Chem. Int. Ed.* **2020**, *59*, 1018–1029; *Angew. Chem.* **2020**, *132*, 1030–1041; b) C. Bolm, J. G. Hernández, *Angew. Chem. Int. Ed.* **2019**, *58*, 3285–3299; *Angew. Chem.* **2019**, *131*, 3320–3335.

[34] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563.

[35] R. Poreddy, C. Engelbrekt, A. Riisager, *Catal. Sci. Technol.* **2015**, *5*, 2467–2477.

[36] a) M. De Amici, P. Conti, G. Vistoli, G. Carrea, G. Ottolina, C. De Micheli, *Med. Chem. Res.* **2001**, *10*, 615–633; b) S. H. Watterson, A. J. Dyckman, W. J. Pitts, S. H. Spergel, *World Intellectual Property Organization* WO 2010/085581 A1; c) I. Diamond, D. Overstreet,

World Intellectual Property Organization, WO 2009/061924 A2.
[37] L. Cecchi, F. De Sarlo, F. Machetti, *Chem. Eur. J.* **2008**, *14*, 7903–7912.
[38] P. T. Anastas, J. B. Zimmermann, *Environ. Sci. Technol.* **2003**, *37*, 94 A-101 A.
[39] Y.-T. Li, C.-L. Chen, Y.-Y. Hsu, H.-C. Hsu, Y. Chi, B.-S. Chen, W.-H. Liu, C.-H. Lai, T.-Y. Lin, P.-T. Chou, *Tetrahedron* **2010**, *66*, 4223–4229.
[40] a) K. Kamata, S. Yamaguchi, M. Kotani, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2008**, *120*, 2441–2444; b) Y. Wang, J. Liu, C. Xia, *Adv. Synth. Catal.* **2011**, *353*, 1534–1542.
[41] The dehydrobromination of β-bromostyrene requires high temperature in presence of a strong base, see: J. C. Hessler, *Org. Synth.* **1922**, *2*, 67.
[42] J. M. Pérez, D. J. Ramón, *ACS Sustainable Chem. Eng.* **2015**, 3, 2343–2349.
[43] R. G. Chary, G. R. Reddy, Y. S. S. Ganesh, K. V. Prasad, A. Raghunadh, T. Krishna, S. Mukherjee, M. Pal, *Adv. Synth. Catal.* **2014**, *356*, 160–164.
[44] V. I. Potkin, S. K. Petkevich, A. S. Lyakhov, L. S. Ivashkevich, *Synthesis* **2013**, *45*, 0260–0264.
[45] D. Simoni, F. P. Invidiata, R. Rondanin, S. Grimaudo, G. Cannizzo, E. Barbusca, F. Porretto, N. D'Alessandro, M. Tolomeo, *J. Med. Chem.* **1999**, *42*, 4961–4969.
[46] P. Gao, H.-X. Li, X.-H. Hao, D.-P. Jin, D.-Q. Chen, X.-B. Yan, X.-X. Wu, X.-R. Song, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 6298–6301.
[47] V. G. Desai, S. R. Naik, K. L. Dhumaskar, *Synth. Commun.* **2014**, *44*, 1453–1460.
[48] Y. Li, M. Gao, B. Liu, B. Xu, *Org. Chem. Front.* **2017**, *4*, 445–449.
[49] Z. Lai, Z. Li, Y. Liu, P. Yang, X. Fang, W. Zhang, B. Liu, H. Chang, H. Xu, Y. Xu, *J. Org. Chem.* **2018**, *83*, 145–153.
[50] X.-D. Wang, L.-H. Zhu, P. Liu, X.-Y. Wang, H.-Y. Yuan, Y.-L. Zhao, *J. Org. Chem.* **2019**, *84*, 16214–16221.

RESEARCH ARTICLE

Mechanochemistry Enabled Construction of Isoxazole Skeleton *via* CuO Nanoparticles Catalyzed Intermolecular Dehydrohalogenative Annulation

Adv. Synth. Catal. **2021**, *363*, 1 – 13

M. Vadivelu, S. Sampath, K. Muthu, K. Karthikeyan*, C. Praveen*