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# Solvent-free synthesis of 3,5-isoxazoles via 1,3-dipolar cycloaddition of terminal alkynes and hydroxyimidoyl chlorides over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ball-milling conditions†

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Scalable, solvent-free synthesis of 3,5-isoxazoles under ball-milling conditions has been developed. The proposed methodology allows the synthesis of 3,5-isoxazoles in moderate to excellent yields from terminal alkynes and hydroxyimidoyl chlorides, using a recyclable Cu/Al<sub>2</sub>O<sub>3</sub> nanocomposite catalyst. Furthermore, the proposed conditions are reproducible to a 1.0-gram scale without further milling time variations.

The addition of oxygen or nitrogen-containing heterocycles in drug candidates has become a common feature of the recently approved drugs by the FDA.<sup>1,2</sup> In particular, isoxazoles are common molecular scaffolds employed in medicinal chemistry due to the non-covalent interactions such as hydrogen bonding (through the N) and  $\pi$ - $\pi$  stacking (by the unsaturated 5-membered ring).<sup>3-6</sup> Within the isoxazole family, 3,5-isoxazoles (**1**) are regularly utilized as pharmacophores in medicinal chemistry.<sup>2,5,6</sup> Selected examples including muscimol (GABA<sub>A</sub> agonist), isocarboxazid (antidepressant), isoxicam (anti-inflammatory), berzosertib (ATR kinase inhibitor), and sulfamethoxazole (antibiotic) are highlighted in Fig. 1.<sup>7-10</sup>

Various methodologies to synthesize 3,5-isoxazoles have been developed over the years.<sup>7,9,11-13</sup> Specifically, 1,3-dipolar cycloaddition between terminal alkynes (**2**) and nitrile oxides (**4**) formed *in situ* by deprotonation of hydroxyimidoyl chlorides (**3**) is a standard route to access 3,5-isoxazoles (**1**) (Fig. 2).<sup>7,9,14</sup> Recent reports have sought to mitigate the environmental impact of this reaction by performing 1,3-dipolar cycloaddition under solvent-free conditions, using green solvents such as water or ionic liquids, under metal-free conditions, or using mild oxidants.<sup>14-28</sup> However, these methodologies have a low atom economy, have a higher hazardous waste production, and are less energy efficient. Therefore, developing a greener methodology that enables rapid and efficient access to these scaffolds is highly desirable.

Mechanochemistry has been recognized as an environmentally friendly technique as reactions can be performed under solvent-free conditions. Additionally, in some instances, work-up and purification are simplified or absent from procedures, and the process consumes less energy than other solution-based techniques.<sup>29-33</sup> The use of mechanochemical techniques to synthesize isoxazoles is limited. Sherin *et al.* reported a synthesis of 3,5-isoxazoles (**7**) by grinding in a mortar and pestle curcumin derivatives (**5**), hydroxylamine (**6**), and substoichiometric amounts of acetic acid to form the 3,5-isoxazole (**7**) in short times and excellent yields (Fig. 3a).<sup>34</sup> Likewise, Xu *et al.* studied the synthesis of trisubstituted isoxazoles (**10**) via 1,3-dipolar cycloaddition of *N*-hydroxybenzimidoyl chlorides (**8**) and *N*-substituted  $\beta$ -enamino carbonyl (**9**)

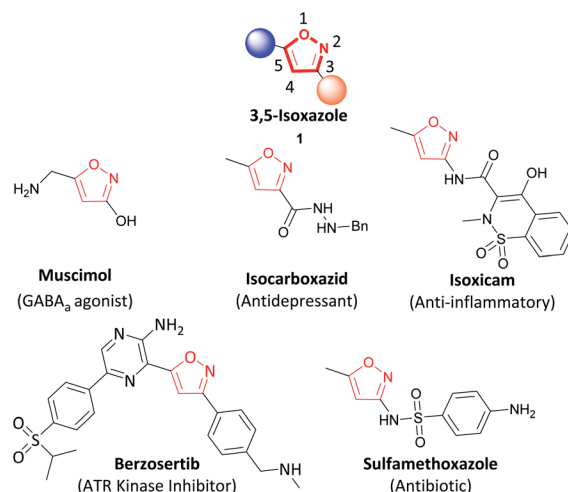


Fig. 1 Examples of isoxazoles with pharmacological activity.

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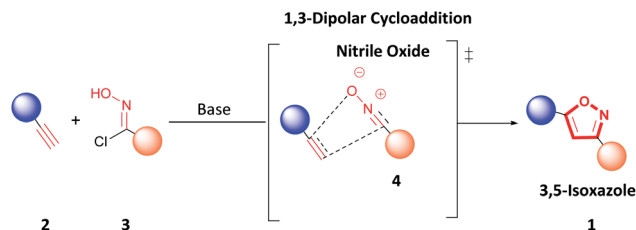
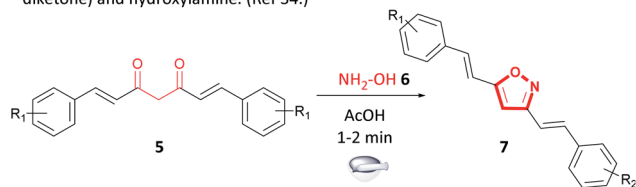
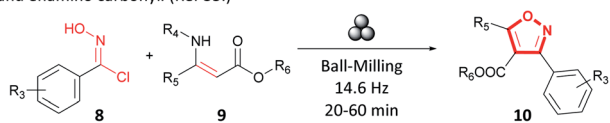


Fig. 2 1,3-Dipolar cycloaddition of terminal alkynes and nitrile oxides.

a) Mechanochemical synthesis of 3,5-isoxazoles from Curcumin derivative (1,3-diketone) and hydroxylamine. (Ref 34.)



b) Mechanochemical synthesis of isoxazoles from N-hydroxybenzimidoyl chlorides and enamino carbonyl. (Ref 35.)



c) **This work:** Mechanochemical synthesis of 3,5-isoxazole from alkynes and  $\alpha$ -chlorooximes.

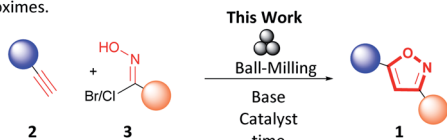


Fig. 3 Previously reported synthesis of isoxazoles.

compounds by ball-milling (Fig. 3b) in high yields, short reaction times, in the absence of catalyst and liquid additives.<sup>35</sup> To our knowledge, mechanochemical synthesis of 3,5-isoxazoles (1) from terminal alkynes (2) and hydroxyimidoxy chloride (3) has not been reported (Fig. 3c). The proposed methodology employs a planetary ball-milling technique that provides a route to access in large scale, short reaction times, and high atom economy the corresponding 3,5-isoxazoles (1). Additionally, it utilizes synthetically accessible or commercially available motifs such as terminal alkynes (2) and hydroxyimidoxy chlorides (3) that are recurrent or easily installed in many substrates. Herein, we report a mechanochemical 1,3-dipolar cycloaddition using the planetary ball-mill to synthesize a wide range 3,5-isoxazoles from a broad library of alkynes and (*E,Z*)-*N*-hydroxy-4-nitrobenzimidoyl chloride (3a), ethyl (*E,Z*)-2-chloro-2-(hydroxyimino)acetate (3b), hydroxycarbonimidic dibromide (3c), or (*E,Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride (3d) in moderate to excellent yields, in short reaction time, and with less waste production than in solution based reactions (Fig. 3c).

We began our investigation by performing an optimisation of the 1,3-dipolar cycloaddition reaction between alkyne 2a and hydroxyimidoxy chlorides 3a by milling the selected substrates in a stainless-steel (SS) jar in the planetary ball-mill to obtain

Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Changes from optimized conditions	Yield <sup>b</sup> (%) of 1a
1	None	72
2	Milling for 10 min, 7 SS balls	59
3	Milling for 15 min 7 SS balls	64
4	Milling for 30 min	58
5	Milling for 40 min	60
6	Using 1.0 equiv. of 3a	65
7	Using 2.0 equiv. of 3a	57
8	Using K <sub>2</sub> CO <sub>3</sub>	71
9	Using Cs <sub>2</sub> CO <sub>3</sub>	71
10	Using CaCO <sub>3</sub>	44
11	Using Ag <sub>2</sub> CO <sub>3</sub>	18
12	Using NEt <sub>3</sub>	N.R.

<sup>a</sup> Reaction Conditions: 0.166 mmol of 2a, 0.250 mmol of 3a, 0.332 mmol of Na<sub>2</sub>CO<sub>3</sub>, SS beaker (50 mL capacity), 8 × SS milling balls (10 mm diameter), 20 min milling, 60 Hz. <sup>b</sup> <sup>1</sup>H-NMR yields were measured using 1,3,5-trimethoxybenzene as an internal standard.

3,5-isoxazole 1a (Table 1). During the optimization, the effect of milling time, amount of milling media, base, and equivalents of hydroxyimidoxy chlorides were studied to obtain the highest yield of 3,5-isoxazole 1a (Table 1). Optimization revealed the combination of 1.0 equivalent of alkyne 2a, 1.5 equivalents of hydroxyimidoxy chlorides 3a, and 2.0 equivalents of Na<sub>2</sub>CO<sub>3</sub> while milling for 20 minutes with 8 SS balls provided the most effective conditions (Table 1, entry 1). Our first control experiments focused on optimizing the milling time (Table 1, entries 2–5). Milling the reagents for less than 20 minutes affords lower product yields (Table 1, entries 2 and 3). Conversely, milling the reagents longer than 20 minutes leads to a decrease in yield to about 60% (Table 1, entries 4 and 5). The strong abrasion of the SS milling media for extended periods could lead to a ring-opening by a reduction of the N–O to yield  $\beta$ -keto-enamine.<sup>36,37</sup>

Having optimized the milling time, we next attempted to improve the yield by varying the equivalents of hydroxyimidoxy chlorides 3a since reaction stoichiometry has been shown to impact the product formed during mechanochemical reactions.<sup>38,39</sup> 3,5-isoxazole 1a was obtained in lower yields when using equimolar amounts alkyne 2a to hydroxyimidoxy chlorides 3a (entry 6, Table 1). Because nitrile oxides rapidly dimerize to form furoxans by a competing 1,3-dipolar cycloaddition.<sup>40–45</sup> Likewise, increasing the equivalents of 18a from 1.0 to 2.0 equivalents lowered the yield of the reaction (entry 7, Table 1). We obtained the highest yield with 1.5 equivalents of the hydroxyimidoxy chlorides of 3a, and these conditions were used for further experiments (entry 1, Table 1). We next studied the effect of diverse carbonated bases in the reaction. We observed that changing the base did not improve the yield of the reaction, and Ag<sub>2</sub>CO<sub>3</sub> was most detrimental to the reaction as it



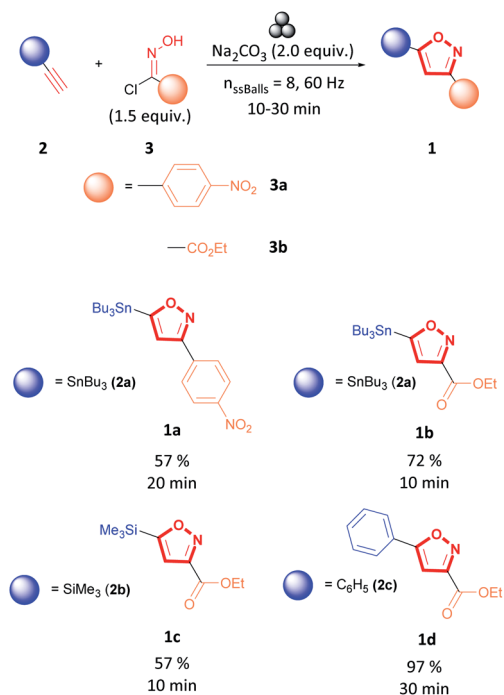


Fig. 4 Catalyst-free mechanochemical synthesis of 3,5-isoxazoles.

promoted furoxan formation (entries 8–11, Table 1).<sup>46,47</sup> Using triethylamine ( $\text{NET}_3$ ) proved impractical as the addition of  $\text{NET}_3$  to hydroxyimidoxy chlorides was highly exothermic in the absence of solvent (entry 12, Table 1).

During the screening, we observed that milling time influences the reaction yield.<sup>35,48</sup> Therefore, a milling time optimization for other alkyne and hydroxyimidoxy chloride combinations revealed that the most optimal milling time was determined to be between 10 and 30 minutes (see ESI† for milling time optimizations).

As shown in Fig. 4, stannanyl isoxazole **1a** and **1b**, silyl isoxazole **1c**, and phenyl isoxazole **1d** were synthesized with satisfactory yields under the proposed conditions. To explain these results, we suggest an electronic argument. The electron-withdrawing character of the metal substituents, stannyl or silyl of alkyne **2a** and **2b**, respectively, accelerates the reaction by deactivating the alkyne moiety.<sup>49–51</sup> It is observed that alkyne **2a** bearing the alkylstannane substituent has a more pronounced effect than the alkyne with the silyl substituent (**2b**). Therefore, alkyne **2a** was the most reactive as it reacted with hydroxyimidoxy chlorides **3a** and **3b** to synthesize 3,5-isoxazole **1a** and **1b** respectively, in short times and excellent yields (Fig. 4). On the other hand, ethynyltrimethylsilane (**2b**) was less reactive as it could only react with a more labile hydroxyimidoxy chlorides **3b** to form 3,5-isoxazole **1c** (Fig. 4). Comparably, we suggest that the phenyl substituent of alkyne **1c** increases the polarizability of the molecule, resulting in deactivating the alkyne moiety. As a result, phenylacetylene (**1c**) reacted in excellent yields with hydroxyimidoxy chlorides **1b**.<sup>42</sup> In addition, we observed that the electronic nature of the hydroxyimidoxy chloride substituent affects the reactivity of the nitrile oxide dipole. Hydroxyimidoxy

Table 2 Effect of copper(II) in the synthesis of 3,5-isoxazoles<sup>ac</sup>

Entry	Cu(II)	Equivalents	Time (min)	Yield <sup>b</sup> (%) <b>19e</b>
1	Cu/ $\text{Al}_2\text{O}_3$	0.14 of Cu(II)	10	73
			20	76
			30	79
			40	64
			50	56
2	$\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$	0.1	30	78
3	$\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$	1.0	30	84
4	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	1.0	30	88
5	$\text{Cu}(\text{OTf})_2$	1.0	30	76
6	$\text{CuCl}_2 \cdot \text{H}_2\text{O}$	1.0	30	76
7	$\text{Cu}_2\text{CO}_3(\text{OH})_2$	2.0	30	36

<sup>a</sup> Reaction conditions: 0.220 mmol of **2d**, 0.330 mmol of **3b**, 0.220 mmol of  $\text{Na}_2\text{CO}_3$ , 0.440 mmol (14 mol%) of  $\text{Cu}/\text{Al}_2\text{O}_3$ , SS beaker (50 mL capacity),  $8 \times$  SS milling balls (10 mm diameter), 60 Hz. <sup>b</sup>  $^1\text{H}$  NMR yields were measured using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> See ESI for solid-state characterization by FT-IR and MALDI-TOF-MS of reaction crude **1e**.

chlorides **3a** containing an aromatic substituent with strong electron-withdrawing groups decreased the reactivity of the nitrile oxide.<sup>52,53</sup> Consequently, the nitrile oxide synthesized *in situ* from hydroxyimidoxy chlorides **3a** could only react with tributyl(ethynyl)stannane (**2a**). On the other hand, hydroxyimidoxy chlorides **3b** was the most reactive due to the bearing of a weaker electron-withdrawing group such as the ester functional group.<sup>43,52</sup> Unfortunately, other alkynes containing substituents such as esters, pyridines, or substituted arenes were not tolerated under these conditions. Previous reports demonstrated the effect of copper catalyst or copper additives to accelerate the reaction and obtain the 3,5-isoxazoles in a regio-selective manner.<sup>15,53–59</sup> Therefore, we aimed to investigate the effect of copper additives or catalysts on this reaction.

Although the mechanochemical synthesis of 3,5-isoxazoles using copper(II) catalyst is unprecedented, 1,2,3-triazoles have been synthesized in this way with copper(II) salts and copper(II)

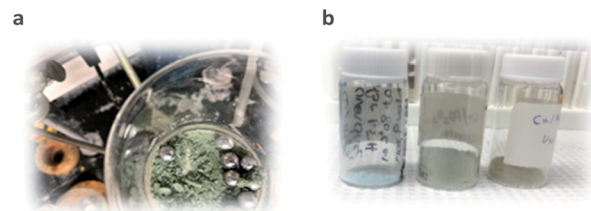


Fig. 5 (a) Filtration of the  $\text{Cu}/\text{Al}_2\text{O}_3$  catalyst after the first run. (b) Colour change of the  $\text{Cu}/\text{Al}_2\text{O}_3$  catalyst after recycling. From left to right. (left) Fresh catalyst: blue. (middle) First recycle: green. (right) Second recycle: brown.



ions in alumina nanocomposites ( $\text{Cu}/\text{Al}_2\text{O}_3$ ).<sup>60,61</sup> We investigated the effect of  $\text{Cu}/\text{Al}_2\text{O}_3$  (see ESI† for XPS spectrum) and copper salts using methyl propiolate (**2d**) and (*E,Z*)-2-chloro-2-(hydroxyimino)acetate (**3b**) as model substrates (Table 2).

We observed a significant increase in yield and regioselective control when using sub-stoichiometric amounts of copper (0.14 equivalents or 14 mol%) of  $\text{Cu}/\text{Al}_2\text{O}_3$  or 10 mol% of  $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$  while milling the reagents for 30 minutes (entries 1 and 2, Table 2). Irreproducible yields were obtained by decreasing the catalytic loading to 7 mol% of  $\text{Cu}/\text{Al}_2\text{O}_3$ . In contrast, when the equivalents of  $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$  were increased to 1.0 equivalent, we observed no significant increase in yield (entry 3, Table 2). Additionally, when investigating the effect of the counter anion on the copper(II), it was observed that  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  performs similarly to  $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$  (entry 4, Table 2), while  $\text{Cu}(\text{OTf})_2$  and  $\text{CuCl}_2 \cdot \text{H}_2\text{O}$  produced lower yields (entries 5 and 6, Table 2). Substituting  $\text{Na}_2\text{CO}_3$  with

$\text{Cu}_2\text{CO}_3(\text{OH})_2$  lowered the yield drastically (entry 7, Table 2). Interestingly, the addition of copper salts did not lead to homocoupling of the alkyne moiety by the Glaser reaction.<sup>62–64</sup>

We decided to continue our investigations using  $\text{Cu}/\text{Al}_2\text{O}_3$  as the catalyst can be filtered and washed with solvent, thereby facilitating catalyst recovery and recycling (Fig. 5).<sup>60</sup>

The  $\text{Cu}/\text{Al}_2\text{O}_3$  catalyst effect was not exclusively beneficial for the cycloaddition with methyl propiolate (**2d**) (3,5-isoxazole **1e**, Fig. 6). This system improves the reactivity of hydroxyimidoxy chlorides **3a**, **3b**, **3c**, and **3d** and other alkynes inaccessible under copper-free conditions, thus allowing access to a broader library of 3,5-isoxazoles (Fig. 6). Moreover, the presence of  $\text{Cu}/\text{Al}_2\text{O}_3$  nanocomposite as part of the reaction conditions is not impaired by the presence of labile substituents such as silanes (**1c**, **f–h**), alkyl halides (**1i–j**), and boronic esters (**1n**) (Fig. 6). However, the presence of alkyl stannane substituents in the dipolarophile (**2a**) was not tolerated with  $\text{Cu}/\text{Al}_2\text{O}_3$  catalyst, and

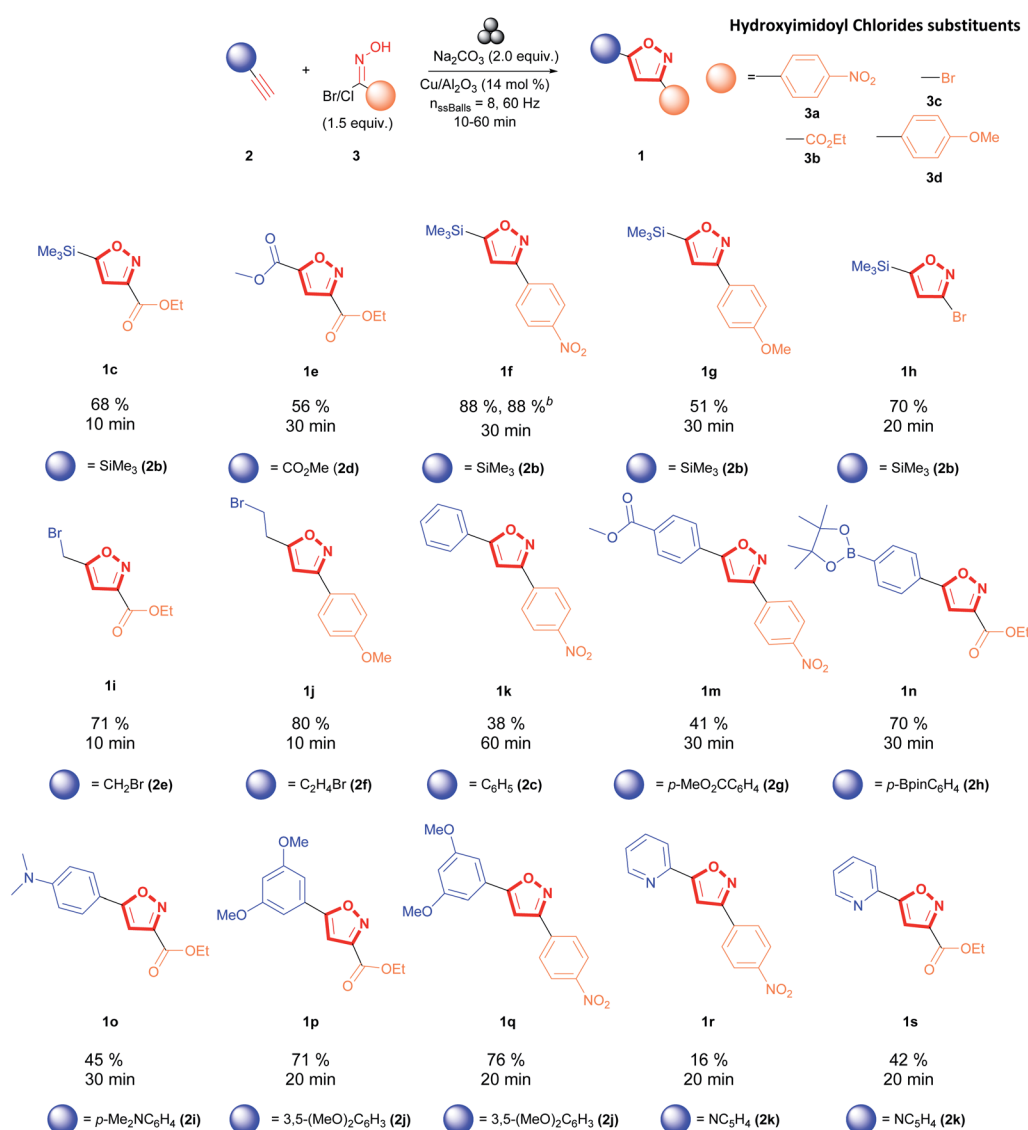


Fig. 6 Mechanochemical synthesis of 3,5-isoxazoles reaction scope. <sup>a</sup>All shown yields are isolated yields. <sup>b</sup>Reaction performed in 1.0-gram scale.





no product was observed. Furthermore, Cu/Al<sub>2</sub>O<sub>3</sub> enhances the reactivity of dipolarophiles bearing arenes with electron-donating substituents (EDG) (**1o–q**) and electron-withdrawing groups (EWG) (**1n**, **1r–2**) when coupled with hydroxyimidoil chlorides **3a** and **3b**. Additionally, pyridine substituents were more reactive towards the more reactive hydroxyimidoil chlorides (**3b**) (3,5-isoxazole **1s**, Fig. 6). Ethynyltrimethylsilane (**1c**) reacted efficiently with hydroxyimidoil chlorides bearing EWG (**3a**, **3b**, and **3c**) to form the respective isoxazoles **1c**, **1f**, and **1h**, where silyl isoxazole **1c** is obtained in higher yields compared to copper-free conditions (**1c**, Fig. 4). Hydroxyimidoil chloride bearing EDG (**3d**); resulted incompatible with terminal alkyne **2b** and silyl isoxazole **1g** was obtained in lower yields than with EWG in the hydroxyimidoil chloride. However, terminal alkynes having an aliphatic substituent (**2e** and **2f**) showed greater reactivity towards hydroxyimidoil chloride (**3d**) bearing EDG; consequently, aliphatic isoxazole **1j** was obtained in higher yields than **1i**. Then, we evaluated the impact of our conditions in the synthesis of 3,5-isoxazole **1f** on a 1.0-gram scale (10.18 mmol). We were pleased to observe that the optimized Cu/Al<sub>2</sub>O<sub>3</sub> conditions can be translated with excellent reproducibility from a 100 mg scale to a 1.0-gram scale without extending the milling time of the reagents (Fig. 6).

The practicality of the proposed methodology allows the recovery of Cu/Al<sub>2</sub>O<sub>3</sub> nanocomposite catalyst directly after the milling of the reagents. In addition, the catalyst recovery allowed investigating the reusability of the recovered catalyst. The Cu/Al<sub>2</sub>O<sub>3</sub> was reused on four occasions, and it was observed that 3,5-isoxazole **1f** was obtained successfully with only a minimal drop in yield with each subsequent use for the first two recycling cycles (Fig. 7). The decrease in yield is explained by the decrease in the concentration of active Cu species in the Cu/Al<sub>2</sub>O<sub>3</sub> nanocomposite (see ESI†). ICP-MS analysis demonstrates that the Cu concentration of the first recycling represents a decrease of 1.24-fold (with respect to the fresh catalyst); thus, similar yields are obtained compared to the fresh catalyst (Fig. 7). However, the decrease in Cu concentration becomes more substantial for the second and third reuse with a decrease of 2.42 and 6.48-fold, respectively. Therefore, a considerable decrease in the yield of isoxazole **1f** is observed. Furthermore,

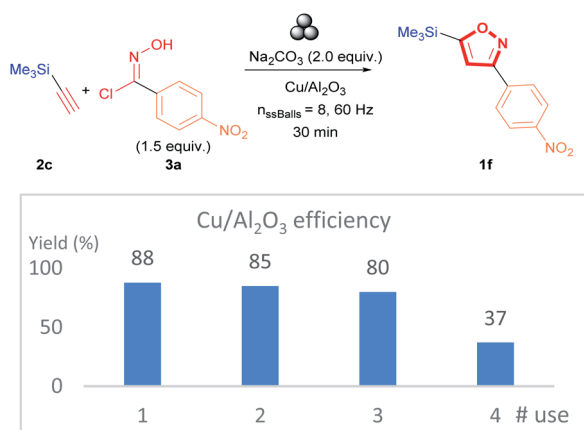


Fig. 7 Cu/Al<sub>2</sub>O<sub>3</sub> efficiency study in the synthesis of 3,5-isoxazole **1f**.

a change in the oxidation state and the bonding of the supported Cu(II) ions. X-ray Photoelectron Spectroscopy (XPS) analysis of the first and second recycled catalyst reveals that the characteristic satellite signals of Cu(II) found at about 942.8 eV are weak while the satellite signal at 963.2 eV is absent. Additionally, the 2p<sub>3/2</sub> signal at about 933–934 eV is wider than in the fresh sample (see ESI for XPS spectra of the fresh, Fig. S3 for first recycling and Fig. S4† for second recycling). These observations suggest that the supported Cu(II) is reduced to Cu(0) and CuO is formed with each subsequent recycling.<sup>65–67</sup>

Lastly, we evaluated the sustainability of the proposed mechanochemical 1,3-dipolar cycloaddition conditions by comparing *E*-factor for the synthesis of 3,5 isoxazoles **1d** and **1f** to previously reported solution-based conditions (Fig. 8).<sup>54,68</sup> Using *E*-factor, the values calculated for the planetary ball milling conditions (pathway **a** and **c**, Fig. 8) demonstrate the sustainability of this methodology compared to solution-based reactions (pathway **b** and **d**) (see ESI† for calculations). With our conditions, the absence of organic solvent is the most significant factor contributing to lowering the *E*-factor.<sup>69</sup> Time differences were also another factor of comparison with previously reported solution-based conditions. Our mechanochemical conditions did not surpass 60 minutes, contrary to the reported

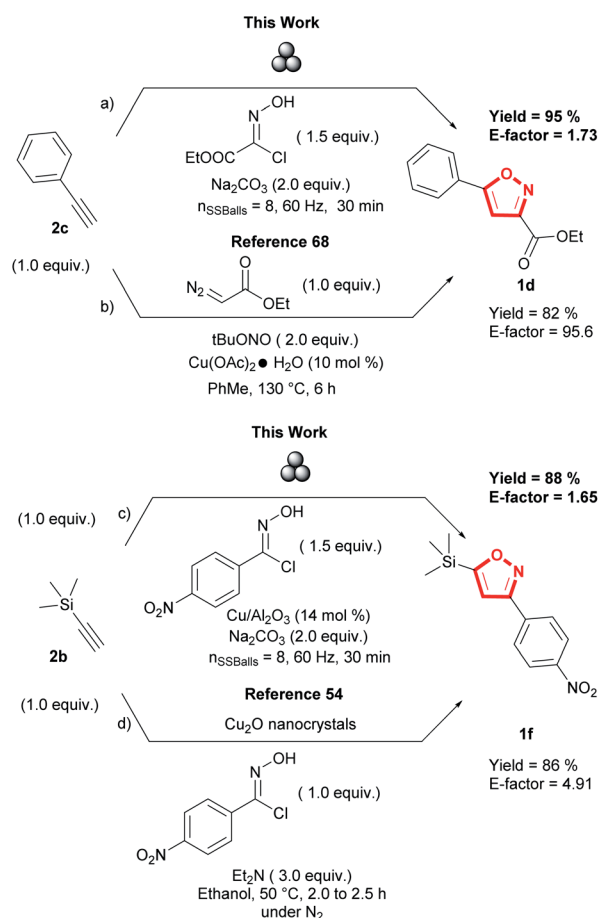


Fig. 8 Comparative green metrics of the proposed methodology to previously reported solution-based methodologies.

solution-based conditions that require at least two hours to synthesize the desired 3,5-isoxazoles. Furthermore, our conditions did not show any sensitivity to oxygen or moisture present in the air as all reactions were performed in an open atmosphere.

## Conclusions

In conclusion, we have developed a scalable, solvent-free, and efficient mechanochemical synthesis of 3,5-isoxazoles *via* 1,3-dipolar cycloaddition from terminal alkynes and hydroxyimido-yl chlorides. We presented two methodologies; a catalyst-free methodology which scopes extended to dipolarophiles bearing alkyl stannane substituent. Under catalyst-free conditions, ethynyltrimethylsilane (**2c**) and phenylacetylene (**2d**) reacted satisfactorily with (*E,Z*)-2-chloro-2-(hydroxyimino) acetate (**3b**). Additionally, a Cu/Al<sub>2</sub>O<sub>3</sub> mediated methodology allowed to react a broader range of dipolarophiles bearing electron-donating or electron-withdrawing substituents with any hydroxyimido-yl chloride. The reported methodology was scalable to a 1.0-gram scale without additional milling time variations. The Cu/Al<sub>2</sub>O<sub>3</sub> catalyst was demonstrated to easily be recycled and reused three times with only a slight reduction in yield. The reported conditions require shorter reaction times, they had a lower *E*-factor, and no prevention was taken to air or moisture, making these methodologies less environmentally harmful and more practical than previously reported solution-based methodologies.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 2 M. D. Delost, D. T. Smith, B. J. Anderson and J. T. Njardarson, *J. Med. Chem.*, 2018, **61**, 10996–11020.
- 3 K. P. Rakesh, C. S. Shantharam, M. B. Sridhara, H. M. Manukumar and H. L. Qin, *Med. Chem. Commun.*, 2017, **8**, 2023–2039.
- 4 P. P. Sharp, J. M. Garnier, D. C. S. Huang and C. J. Burns, *Med. Chem. Commun.*, 2014, **5**, 1834–1842.
- 5 A. Sysak and B. Obmińska-Mrukowicz, *Eur. J. Med. Chem.*, 2017, **137**, 292–309.
- 6 J. Zhu, J. Mo, H. Lin, Y. Chen and H. Sun, *Bioorg. Med. Chem.*, 2018, **26**, 3065–3075.
- 7 M. Kim, Y. S. Hwang, W. Cho and S. B. Park, *ACS Comb. Sci.*, 2017, **19**, 407–413.
- 8 L. Gorecki, M. Andrs, M. Rezacova and J. Korabecny, *Pharmacol. Ther.*, 2020, **210**, 107518.
- 9 F. Hu and M. Szostak, *Adv. Synth. Catal.*, 2015, **357**, 2583–2614.
- 10 H. Zinnes, J. C. Sircar, N. Lindo, M. L. Schwartz, A. C. Fabian, J. Shavel, C. F. Kasulani, J. D. Genzer, C. Lutomski and G. DiPasquale, *J. Med. Chem.*, 1982, **25**, 12–18.
- 11 S. Roscales and J. Plumet, *Org. Biomol. Chem.*, 2018, **16**, 8446–8461.
- 12 L. Claisen and O. Lowman, *Ber. Dtsch. Chem. Ges.*, 1888, **21**, 1149–1157.
- 13 J. Li, Z. Lin, W. Wu and H. Jiang, *Org. Chem. Front.*, 2020, **7**, 2325–2348.
- 14 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210–216.
- 15 T. V. Hansen, P. Wu and V. V. Fokin, *J. Org. Chem.*, 2005, **70**, 7761–7764.
- 16 J. Li, J. Yu, W. Xiong, H. Tang, M. Hu, W. Wu and H. Jiang, *Green Chem.*, 2020, **22**, 465–470.
- 17 D. Wang, F. Zhang, F. Xiao and G. J. Deng, *Org. Biomol. Chem.*, 2019, **17**, 9163–9168.
- 18 D. R. Meena, B. Maiti and K. Chanda, *Tetrahedron Lett.*, 2016, **57**, 5514–5517.
- 19 S. B. Bharate, A. K. Padala, B. A. Dar, R. R. Yadav, B. Singh and R. A. Vishwakarma, *Tetrahedron Lett.*, 2013, **54**, 3558–3561.
- 20 J. M. Pérez and D. J. Ramón, *ACS Sustainable Chem. Eng.*, 2015, **3**, 2343–2349.
- 21 A. M. Jawalekar, E. Reubsaet, F. Rutjes and F. van Delft, *Chem. Commun.*, 2011, **47**, 3198–3200.
- 22 M. Vadivelu, S. Sampath, K. Muthu, K. Karthikeyan and C. Praveen, *J. Org. Chem.*, 2019, **84**, 13636–13645.
- 23 A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskae and V. V. Zhdankin, *Org. Lett.*, 2013, **15**, 4010–4013.
- 24 L. Lin, J. Zhang and R. Wang, *Asian J. Org. Chem.*, 2012, **1**, 222–225.
- 25 S. Mohammed, R. A. Vishwakarma and S. B. Bharate, *RSC Adv.*, 2015, **5**, 3470–3473.
- 26 C. Kesornpun, T. Aree, C. Mahidol, S. Ruchirawat and P. Kittakoop, *Angew. Chem., Int. Ed.*, 2016, **55**, 3997–4001.
- 27 B. Touaux, F. Texier-Boullet and J. Hamelin, *Heteroat. Chem.*, 1998, **9**, 351–354.
- 28 M. Hu, Z. Lin, J. Li, W. Wu and H. Jiang, *Green Chem.*, 2020, **22**, 5584–5588.
- 29 F. Schneider, T. Szuppa, A. Stolle, B. Ondruschka and H. Hopf, *Green Chem.*, 2009, **11**, 1894–1899.
- 30 D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, **52**, 7760–7781.
- 31 S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin,

- W. C. Shearouse, J. W. Steed, W. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447.
- 32 J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080–3094.
- 33 K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145–2162.
- 34 D. R. Sherin and K. N. Rajasekharan, *Arch. Pharm. Chem. Life Sci.*, 2015, 908–914.
- 35 H. Xu, G. P. Fan, Z. Liu and G. W. Wang, *Tetrahedron*, 2018, **74**, 6607–6611.
- 36 S. Auricchio, A. Bini, E. Pastormerlo and A. M. Truscello, *Tetrahedron*, 1997, **53**, 10911–10920.
- 37 M. J. Rak, N. K. Saadé, T. Friščić and A. Moores, *Green Chem.*, 2014, **16**, 86–89.
- 38 V. Štrukil, D. Margetic, M. D. Igrc, M. Eckert-Maksic and T. Friščić, *Chem. Commun.*, 2012, **48**, 9705–9707.
- 39 J. L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, **3**, 13–19.
- 40 J. W. Bode, Y. Hachisu, T. Matsuura and K. Suzuki, *Tetrahedron Lett.*, 2003, **44**, 3555–3558.
- 41 C. Grundmann and J. M. Dean, *J. Org. Chem.*, 1965, **30**, 2809–2812.
- 42 R. Huigens, *Angew. Chem., Int. Ed.*, 1963, **2**, 633–696.
- 43 C. Grundmann and R. Richter, *J. Org. Chem.*, 1967, **32**, 2308–2312.
- 44 T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366–5412.
- 45 C. Grundmann and S. K. Datta, *J. Org. Chem.*, 1968, **34**, 2016–2018.
- 46 P. F. Pagoria, M. X. Zhang, N. B. Zuckerman, A. J. DeHope and D. A. Parrish, *Chem. Heterocycl. Compd.*, 2017, **53**, 760–778.
- 47 M. X. Zhang, A. J. Dehope and P. F. Pagoria, *Org. Process Res. Dev.*, 2019, **23**, 2527–2531.
- 48 F. Schneider, A. Stolle, B. Ondruschka and H. Hopf, *Org. Process Res. Dev.*, 2009, **13**, 44–48.
- 49 T. Deb, J. Tu and R. M. Franzini, *Chem. Rev.*, 2021, **121**, 6850–6914.
- 50 E. Lukevics and P. Arsenyan, *Chem. Heterocycl. Compd.*, 1998, **34**, 1155–1169.
- 51 D. K. Heldmann and J. Sauer, *Tetrahedron Lett.*, 1997, **38**, 5791–5794.
- 52 M. S. Chiang and J. U. Lowe, *J. Org. Chem.*, 1967, **32**, 1577–1579.
- 53 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210–216.
- 54 K. Chanda, S. Rej and M. H. Huang, *Nanoscale*, 2013, **5**, 12494–12501.
- 55 X. Di Wang, L. H. Zhu, P. Liu, X. Y. Wang, H. Y. Yuan and Y. L. Zhao, *J. Org. Chem.*, 2019, **84**, 16214–16221.
- 56 V. V. S. T. M. Vishwanatha, *J. Heterocycl. Chem.*, 2015, **52**, 1823–1833.
- 57 C. Chen and S. Cui, *J. Org. Chem.*, 2019, **84**, 12157–12164.
- 58 Y. Sun, A. Abdukader, H. Zhang, W. Yang and C. Liu, *RSC Adv.*, 2017, **7**, 55786–55789.
- 59 Y. Li, M. Gao, B. Liu and B. Xu, *Org. Chem. Front.*, 2017, **4**, 445–449.
- 60 N. Mukherjee, S. Ahammed, S. Bhadra and B. C. Ranu, *Green Chem.*, 2013, **15**, 389–397.
- 61 R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild and U. S. Schubert, *Chem. Commun.*, 2011, **47**, 4370–4372.
- 62 K. S. Sindhu and G. Anilkumar, *RSC Adv.*, 2014, **4**, 27867–27887.
- 63 R. Schmidt, R. Thorwirth, T. Szuppa and A. Stolle, *Chem.–Eur. J.*, 2011, **17**, 8129–8138.
- 64 L. Chen, B. E. Lemma, J. S. Rich and J. Mack, *Green Chem.*, 2014, **16**, 1101–1103.
- 65 Y. Wen, W. Huang and B. Wang, *Appl. Surf. Sci.*, 2012, **258**, 2935–2938.
- 66 F. E. López-Suárez, A. Bueno-López, M. J. Illán-Gómez, A. Adamski, B. Ura and J. Trawczynski, *Environ. Sci. Technol.*, 2008, **42**, 7670–7675.
- 67 J. B. Reitz and E. I. Solomon, *J. Am. Chem. Soc.*, 1998, **120**, 11467–11478.
- 68 X. Di Wang, L. H. Zhu, P. Liu, X. Y. Wang, H. Y. Yuan and Y. L. Zhao, *J. Org. Chem.*, 2019, **84**, 16214–16221.
- 69 R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48.

