Mechanochemical Desymmetrization of Unbiased Bis- and Tris-alkynes to Access 3,5-Isoxazoles-Alkyne Adducts and Unsymmetrical Bis-3,5-isoxazoles

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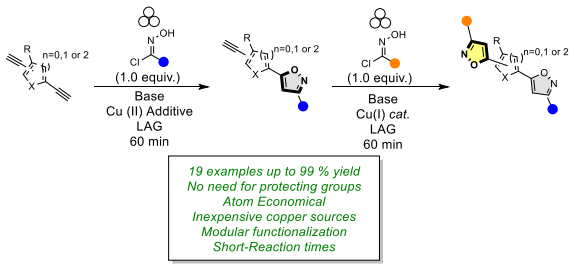


A mechanochemical desymmetrization of symmetrical bis- and tris-alkynes *via* a controlled 1,3-dipolar cycloaddition reaction with nitrile oxide dipoles has been developed. This convenient, efficient, and simple protocol allows access to a wide range of 3,5-isoxazole-alkyne adducts and unsymmetrical bis-3,5-isoxazoles from easily prepared or commercially available symmetrical bis- and tris-alkynes in moderate to excellent yield.

Abstract: A mechanochemical desymmetrization of symmetrical bis- and tris-alkynes *via* a controlled 1,3-dipolar cycloaddition reaction with nitrile oxide dipoles has been developed. This convenient, efficient, and simple protocol allows access to 3,5-isoxazole-alkyne adducts from easily prepared or commercially available symmetrical bis- and tris-alkynes in moderate to excellent yield. The synthetic utility of 3,5-isoxazole-alkyne was demonstrated by developing a route to access β-ketoenamine-alkyne derivatives and the synthesis of unsymmetrical bis-3,5-isoxazoles products in good to excellent yields.

Desymmetrization is a modification that results in the loss of symmetry elements within a molecule, such as a mirror plane, an axis of rotation, or a center of inversion.[1] Desymmetrization strategies are frequently employed in the synthesis of natural products, biologically active substances, and novel organic materials.[2,3] Desymmetrization of symmetrical bis- and tris-alkyne *via* a controlled 1,3-dipolar cycloaddition with nitrile oxide dipoles (NOs) to form 3,5-isoxazole-alkyne adducts has not been thoroughly investigated, and only a few examples have been reported.[4–6] To date, desymmetrization of bis- and tris-alkyne focused on CuAAC (Copper Azide Alkyne Cycloaddition) to form 1,4-triazole-alkyne adducts.[1,7–12] Current desymmetrization strategies to synthesize 3,5-isoxazole-alkyne or azide-alkyne adducts require protecting groups, specific dipoles, and an excess amount of the bis- or tris-alkyne.[1,7–11] The reported approaches suffer from poor atom efficiency due to an excess amount of starting material, the formation of undesired symmetrical by-products, the use of toxic solvents, and laborious methodologies. Therefore, developing sustainable and efficient methodologies to improve atom economy and access novel chemical space is highly desired.[13–17]

Mechanochemical desymmetrization represents a concrete extension to previously developed desymmetrization methodologies.[18,19] For example, Štrukil *et al.* exploited a mechanochemical click desymmetrization of aromatic diamines (**1**) to form mono- and bis-(thioureas) (**2**) in quantitative yields (**Scheme 1a**).[20–22] Similarly, Lanzillotto *et al*. demonstrated a mechanochemical desymmetrization of CDI (1,1'-carbonyldiimidazole) (**3**) to form carbamates (**4**) (**Scheme 1b**).[23] Seo *et al*. reported a step-wise arylation of symmetrical dibromoarenes (**5**) by a mechanochemical Suzuki-Miyaura cross-coupling to obtain unsymmetrical arylated systems (**6**) (**Scheme 1c**).[24] Mechanochemical 1,3-dipolar cycloaddition reactions between NOs generated by dehydrohalogenation of hydroxyimidoyl chloride to desymmetrize symmetrical bis- or tris-alkynes (**7**) remain unstudied (**Scheme 1d**). Herein, we report a selective, scalable, quick, and atom-efficient mechanochemical desymmetrization of bis- and tris-alkynes (**7**) to access 3,5-isoxazole-alkyne adducts (**9**). This protocol demonstrates compatibility for diverse bis- and tris-alkynes (**7**) and does not require protecting groups or excess poly-alkyne substrate. Additionally, we demonstrate the utility of this methodology in the modular synthesis of unsymmetrical bis-3,5-isoxazoles derivatives (**10**) (**Scheme 1d**).

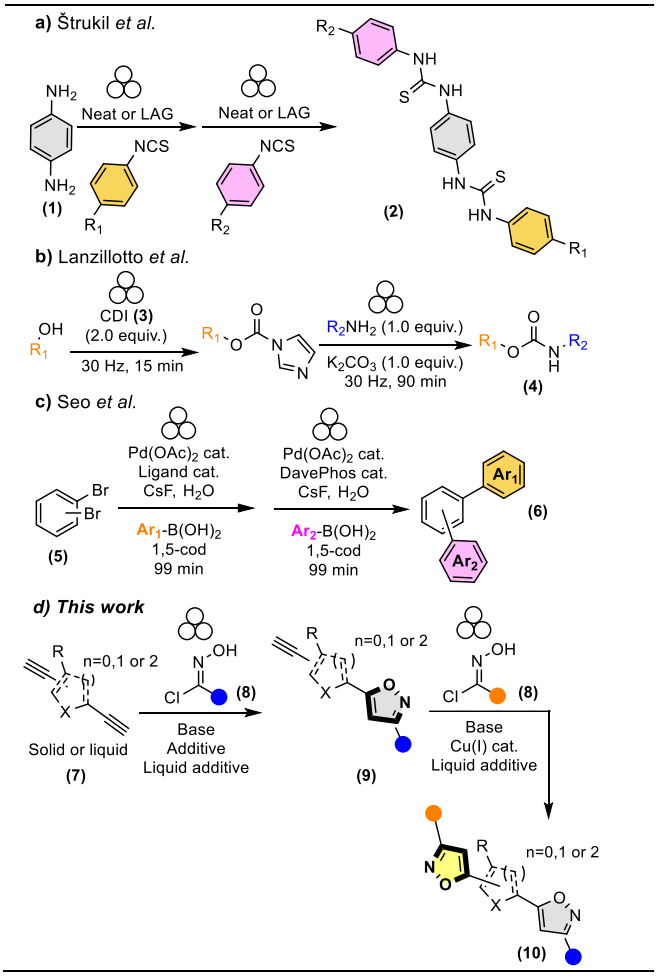


Figure 1. Mechanochemistry in the desymmetrization of symmetric organic molecules.

Our investigations began by optimizing the desymmetrization of the symmetrical solid aromatic bis-alkyne (**7a**) with ester hydroxyimidoil chloride (**8a**) to form the 3,5-isoxazole-alkyne adduct (**9a**) (**Table 1**). All reactions were performed in a Pulverisette 7 mill, with reactants contained in a stainless-steel (SS) jar along with eight SS balls (32 g) of 1 cm diameter for 60 min at 60 Hz (**Table 1, entry 1**). The desired product (**9a**) can be obtained selectively without the need to use an excess of either the aromatic bis-alkyne (7a) or ester hydroxyimidoyl chloride (**8a, Table 1, entries 2-4**).

We attempted to improve the performance of the reaction by screening different additives with Lewis acid character (**entry 5-9, Table 1**). These additives accelerate cycloaddition via π-complexation with the alkyne moiety.[25–29] Using 1.0 equivalent of $Cu(NO_3)_2{\cdot}2.5H_2O$ improves the selectivity favoring the formation of the desired 3,5-isoxazole-alkyne adduct (**9a**) over the undesired symmetrical bis-3,5-isoxazole (**11a**) (**entry 7, Table 1**). Other nanocomposites and metal additives such as Cu/Al_2O_3, $ZnCl_2$, and $IrCl_3{\cdot}xH_2O$ were detrimental to the desymmetrization and promoted the formation of symmetrical bis-3,5-isoxazole (**11a**) or the dimerization of the NOs to obtain undesired furoxans (**entry 6-9**). In addition to the plausible complexation between Cu(II) and the alkyne moiety, $Cu(NO_3)_2{\cdot}2.5H_2O$ may serve as a solid-state diluting agent that homogenizes the mixture, thus

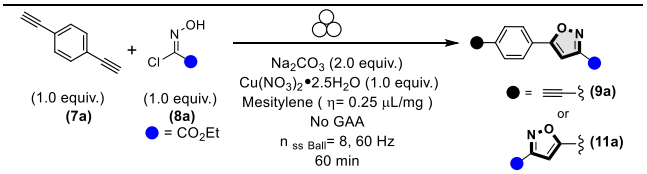
promoting the desymmetrization and the formation of 3,5-isoxazole-alkyne adduct (**9a**).[26,30–34] Increasing substrate dilution by using grinding auxiliary agents (GAAs) such as NaCl, KCl, or Al_2O_3 in combination with $Cu(NO_3)_2{\cdot}2.5H_2O$ were ineffective and the 3,5-isoxazole-alkyne adduct (**9a**) was obtained in lower yields (**entry 10-12**).[30,31,33–36]

We also investigated the effect of liquid-assisted grinding (LAG) in terms of the η parameter (defined as the ratio of the volume of liquid additive µL to the total mass of reactants in mg). LAG has been demonstrated to accelerate mechanochemical reactions by facilitating bulk-mass transfer [30,33,34,37] and was shown to modify and enhance reaction selectivity.[32,33,35–38] An increase in the reaction yield and selectivity for 3,5-isoxazole-alkyne adduct (**9a**) was achieved when using aromatic liquid additives (**entry 1,15-16**), where mesitylene was found to be the most effective additive (**entry 1**). Only 0.25 µL/mg of mesitylene was required and increasing the amount beyond this did not improve the yield and selectivity for the desired adduct (**9a**), while polar and protic liquid additives did not improve the yield or selectivity (**9a**) (**entry 13-14**). These observations suggest that mesitylene has the suitable polarity to accelerate the dehydrohalogenation of the hydroxyimidoyl chloride to form the corresponding NO.[39] The low polarity of the liquid additive accelerates cycloadditions by polarizing the NO and stabilizing the transition state .[40–43] Additionally, π-π stacking between the mesitylene additive and bis-alkyne (**7a**) could promote the activation of the dipolarophile, making it more reactive toward NOs.[40,42,44]

Several reports utilized copper(I) catalysis to accelerate 1,3-dipolarcycloaddition reactions.[45–50] In our case, *in situ* formation of Cu(I) by reduction of Cu(II) salts with sodium ascorbate or addition of Cu(I) complexes in sub-stoichiometric amounts were ineffective and lower selectivity and/or yields for the desired 3,5-isoxazole-alkyne (**9a)** were obtained (see supporting information for details).

Optimizations demonstrated that using equimolar amounts of bis-alkyne (**7a**) and hydroxyimidoyl chloride (**8a**) in combination with 2.0 equivalents of Na_2CO_3, 1.0 equivalent $Cu(NO_3)_2{\cdot}2.5H_2O$ and using mesitylene as a liquid additive were the optimal conditions to desymmetrize aromatic bis-alkyne.

Table 1. Optimization conditions for the mechanochemical desymmetrization of the bis(alkyne) 9a



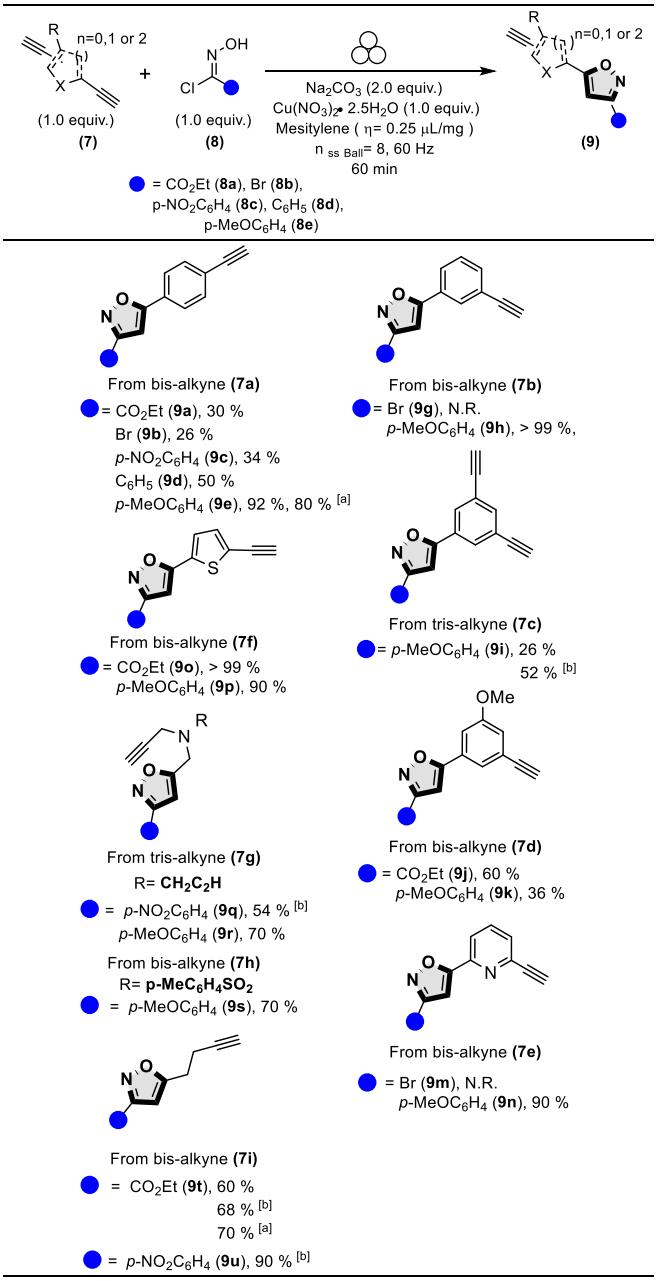
Entry	Condition	Yield [d] (9a)	Yield [d] (11a)	9a:11a [e]
1	No changes [a]	50	1	50:1
Effect of the stoichiometry of 1a and 2a				
2	1.5 equiv. of 8a	30	10	3:1
3	1.1 equiv. of 8a	30	10	3:1
4	2.0 equiv. of 7a	50	1	50:1
Effect of π-type Lewis Acid Additives				
5	No additive	34	4	9:1
6	Cu/Al_2O_3 (14 mol %)	33	10	3:1
7	$Cu(NO_3)_2{\cdot}2.5H_2O$ (1.0 equiv)	30	2	15:1
8	$IrCl_3{\cdot}xH_2O$	25	3	8:1
9	$ZnCl_2$ (1.0 equiv.)	9	4	2:1
Effect of GAA				
10	Al_2O_3 (150 wt %)	9	4	2:1
11	NaCl (150 wt%)	23	2	12:1
12	KCl (150 wt%)	17	2	9:1
Effect of LAG				
13	EtOAc [b]	36	3	12:1
14	EtOH [b]	30	2	15:1
15	Toluene [b], [c]	45	2	20:1
16	Xylenes [c]	45	2	22:1

[a] Reaction conditions: 1a (50 mg, 0.396 mmol, 1.0 equiv.), 2a (60 mg, 0.396 mmol, 1.0 equiv.), $Cu(NO_3)_2{\cdot}2.5H_2O$ (92.1 mg, 0.396, 1.0 equiv.), Na_2CO_3 (84 mg, 0.796 mmol, 2.0 equiv.), mesitylene (η = 0.25 µL/mg, ~72 µL) [b] (η = 0.5 µL/mg, ~144 µL) [c] (η = 0.25 µL/mg, ~72 µL) [d] Yield determined by ^{1}H-NMR using 1,3,5-trimetoxybenzene (TMB) as an internal standard [e] 9a:11a determined by the integration of the crude ^{1}H-NMR signals.

We evaluated the effect of the optimized conditions on different bis- and tris-alkynes (**Scheme 1**). The aromatic bis-alkynes (**7a-f**) displayed a selectivity towards hydroxyimidoyl chlorides of opposing electronic nature. Bis-alkyne systems on an aromatic electron-neutral ring (ENR) (**7a-b**) and electron-deficient ring (EDR) (**7e**) best reacted with hydroxyimidoyl chloride bearing an electron donating group (EDG) (**8e**) where the corresponding 3,5-isoxazole-alkyne adducts (**9e**), (**9h**), and (**9n**) were obtained in excellent yields. When ENR bis-alkyne (**7a**) was reacted with an hydroxyimidoyl chloride bearing electron-neutral groups (ENG) (**8d**), 3,5-isoxazole-alkyne adduct (**9d**) was desymmetrize with an excellent yield, where desymmetrization of bis-alkyne (**7a**) previously was reported to require at least 10 equivalents of bis-alkyne substrate to achieve selectivity for the formation of the 3,5-isoxazole-alkyne adduct.[5] In contrast, when ENR bis-alkynes (**7a-b**) reacted with hydroxyimidoyl chlorides bearing an electron-withdrawing groups (EWG) (**8a-c**), 3,5-isoxazole-alkyne adducts (**9a-c**), (**9g**), and (**9m**) were obtained in low yields. The opposite trend was observed for bis-alkynes on electron-rich rings (ERR) (**7d**) which showed higher reactivity for hydroxyimidoyl chlorides bearing EWG (**8a**). This led to the formation of 3,5-isoxazole-alkyne adduct (**9j**) in higher yields than (**9k**) from a hydroxyimidoyl chloride (**8e**) with an EDG. The electronic discrimination of bis-alkyne systems for hydroxyimidoyl chlorides of opposite electronic nature can be explained by an increase in polarizability for the resulting 3,5-isoxazole-alkyne adduct.[42,51,52]

The physical state of the bis-alkyne influenced the performance of the reaction. Liquid aromatic bis-alkynes were more reactive than solid substrates. This may be due to the limited mass transfer of the solid reagents in contrast to the liquid reagents.[24,33,53–55] This difference was observed when comparing the reactivity of solid ENR bis-alkyne (**7a**) and liquid bis-alkyne (**7b**) when reacted with hydroxyimidoyl chloride (**8e**) bearing an EDG. Synthesis of the 3,5-isoxazole-alkyne adduct (9h) resulted in higher yields than that obtained for (**9e**). A similar trend in reactivity was observed for liquid thiophene bis-alkyne (**7f**). Liquid thiophene bis-alkyne (**7f**) showed equal reactivity for hydroxyimidoyl chlorides bearing an EWG (**8a**) or an EDG (**8e**) to form 3,5-isoxazole-alkyne adducts (**9o**) and (**9p**), respectively**,** with excellent yields without any clear electronic discrimination.

Alkyl poly-alkyne have been investigated in the context of CuAAC due to the possibility of autocatalysis.[56–60] The presence of alkyl-alkyne moieties with a high degree of rotation can stabilize Cu(I) catalysts and accelerate the cycloaddition reaction.[57,58,61] Consequently, we investigated the desymmetrization of alkyl bis- and tris-alkynes to form 3,5-isoxazole-alkyne adducts (**7g-i**). The proposed conditions were demonstrated to be effective for desymmetrizing alkyl bis- and tris-alkynes, and no trend in the electronic properties of the hydroxyimidoyl chlorides was observed. Desymmetrization of liquid tris-alkyne (**7g**) and bis-alkyne (**7i**) demonstrated improved yields by removing the mesitylene liquid additive, producing the corresponding 3,5-isoxazoles-alkyne adducts (**9r-u**) in excellent yields. This effect was also observed in the desymmetrization of the aromatic tris-alkyne (**7c**), where the yield improves in the absence of liquid additive, with 3,5-isoxazole-alkyne (**9i**) obtained in excellent yields. Synthesis of (**9i**) by solution-based protocols required an excess of tris-alkyne (**7c**) and long reaction times to comparable yields and selectivity.[62,63] The scalability of the reaction was investigated for the solid bis-alkyne (**7a**) and liquid bis-alkyne (**7i**). The 1.0 g scale mechanochemical synthesis of 3,5-isoxazole-alkyne adduct (**9e**) from solid aromatic bis-alkyne (**7a**) showed a modest decrease in yield. In contrast, the 1.0 g scale synthesis of 3,5-isoxazole-alkyne adduct (**9t**) from liquid bis-alkyne (**7i**) showed no decrease in yield.

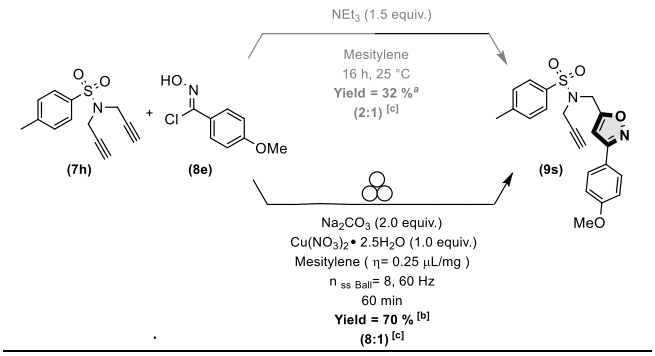


All reported yields are isolated yields. [a] Reaction performed in a 1.0-gram scale of bis(alkyne) substrate. [b] Reaction performed in the absence of LAG.

Figure 2. Scope for the mechanochemical desymmetrization of bis-alkynes and tris-alkynes to form 3,5-isoxazole-alkyne adducts.

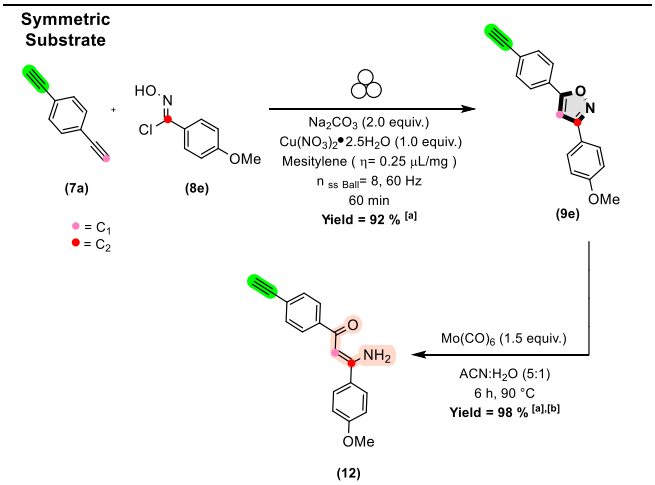
The mechanochemical conditions were compared to solution-based conditions. Reported mechanochemical conditions allowed successful desymmetrization of the bis-alkyne (**7h**) to obtain 3,5-isoxazole-alkyne adduct (**9s**) in 70 % yield and with a superior selectivity for (**9s**) over the symmetrical bis-3,5-isoxazole product only after 60 minutes of milling (**Scheme 3**). Performing the desymmetrization with larger volumes of mesitylene (η =45 μL/mg, 7 mL) yielded 3,5-isoxazole-alkyne adduct (**9s**) in 32 % yield, with poor selectivity after 16 h at room temperature. The described comparison emphasizes the impact of mechanochemistry in

achieving unique reactivity modes to access unexplored chemical space with lower waste production.[24,33,34,55,64,65]



[a] ^{1}H-NMR Yield of **9s** when the reaction is performed by η =45 μL/mg, 7 mL of mesitylene, for a detailed procedure, see section SI (PS3). [b] Isolated yield of product **9s** [c] Ratios of mono to bis-3,5-isoxazole determined by the integration of the crude ^{1}H-NMR.

Figure 3. Comparative effect of mechanochemical and solution-based conditions for the desymmetrization of bis-alkynes and tris-alkynes



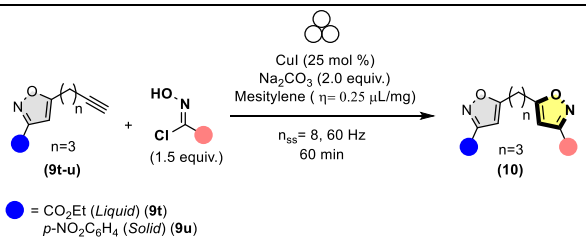
[a] Isolated yield. [b] Reaction Conditions: **9e** (0.18 mmol, 1.0 equiv.), $Mo(CO)_6$ (0.27 mmol, 1.5 equiv.), Acetonitrile:H_2O (5.0 mL: 1.0 mL)

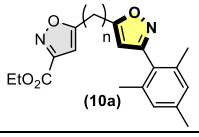
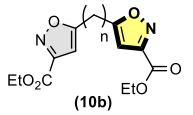
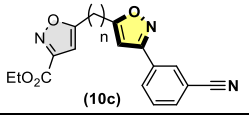
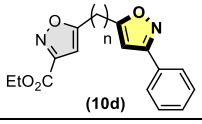
Figure 4. Synthesis of β-ketoenamines-alkyne from symmetrical bis-alkyne systems**.**

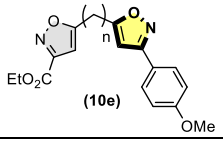
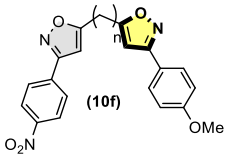
To further expand the chemical space and exploit the formation of a carbon-carbon bond (C_1-C_2) resulting from the cycloaddition, we investigated the N-O bond reduction of the isoxazole to access a β-ketoenamine-alkyne derivative (**Scheme 4**). Although β-ketoenamine motifs are encountered in natural products, materials, and are versatile intermidiates, there are no reports of β-ketoenamine-alkynes.[63,66–75] We studied the reduction of 3,5-isoxazole-alkyne (**9e**) using $Mo(CO)_6$, a conventional reducing agent for isoxazoles. [76–78] We found that N-O reduction to obtain β-ketoenamine (**12**) occurs in excellent yields when performing the reduction at 90 °C and using 1.5 equivalents of $Mo(CO)_6$ (**Scheme 4**). This route achieves a convenient method to access β-ketoenamines with an alkyne handle that can be further modified as required.

The proposed desymmetrization allows for a modular synthesis of unsymmetrical bis-3,5-isoxazoles (**Table 2**) under solvent-free conditions. We observed that the conditions for desymmetrization (**Scheme 1**) and previously reported conditions were ineffective for adding a second 3,5-isoxazole moiety.[28] The reaction was insensitive to electronic properties of reactants as coupling of solid 3,5-isoxazole-alkyne with EWG (**9a**) or EDG (**9e**) with either hydroxyimidoyl chlorides bearing EWG or EDG did not yield the corresponding product and only starting material was recovered. Using alkyl 3,5-isoxazole-alkyne adduct (**9t-u**) demonstrated a improvement in the reaction performance, presumably due to more efficient mixing of the reagents independently of their physical state.[24,55,79,80]. Liquid 3,5-isoxazole-alkyne adduct (**9t**) and sterically bulky hydroxyimidoyl chlorides with catalytic amounts of CuI and mesitylene liquid additive did not form the desired unsymmetrical bis-3,5-isoxazole alkyne (**10a**) (**Table 2**). Improvements in the yield were observed when using less bulky substituents. Synthesis of unsymmetrical bis-3,5-isoxazole (**10b**) was obtained only in moderate yields due to the competing formation of furoxans.[81] Using aromatic hydroxyimidoyl chlorides improves the yield of the reaction. Synthesis of unsymmetrical bis-3,5-isoxazoles (**10c-f**) was obtained in excellent yields independent of the electronic character of the substituent and their physical state. This is likely due to a faster coupling between the aromatic hydroxyimidoyl chlorides and alkyl terminal alkyne (**9t-u**) compared with the dimerization to form furoxans (**Table 2**). [81–84]

Table 2: Synthesis of unsymmetrical bis-3,5-isoxazoles from liquid 3,5-isoxazole-alkyne adduct (9t)



Entry	Structure	Yield (%)[b]
1	 (10a)	N.R.
2	 (10b)	32
3	 (10c)	70
4	 (10d)	96

5	 (10e)	95
6	 (10f)	>99

[a] Reaction Conditions: **9t** (0.517 mmol, 1.0 equiv.), hydroximidoyl chloride (0.755 mmol, 1.5 equiv.), Na_2CO_3 (1.03 mmol, 2.0 equiv.), CuI (0.130 mmol, 25 mol %), mesitylene (η = 0.25 µL/mg). [b] Isolated yield

In conclusion, we developed the first mechanochemical desymmetrization strategy for bis- and tris-alkynes to form 3,5-isoxazole-alkyne adducts without using a large excess of either starting material and by a controlled 1,3-dipolar cycloaddition. The reported conditions were applicable for a range of aromatic and alkyl bis- and tris-alkyne. Late-stage reduction of the 3,5-isoxazole moiety was achieved in high yield and selectivity, allowing a concise route to β-ketoenamine-alkyne derivatives. Furthermore, the mechanochemical desymmetrization allowed access to unsymmetrical bis-3,5-isoxazole from alkyl 3,5-isoxazole-alkyne adducts (**9t-u**) in excellent yields. We believe this protocol can provide efficient access to more intricately functionalized poly-isoxazoles, boron-enaminoketonate, and facilitate the synthesis of natural products.

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Keywords: Organomechanosynthesis • Mechanochemistry • 1,3-dipolar cycloadditions • Desymmetrizations • 3,5-isoxazoles

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