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Mechanochemical multicomponent Ugi-azide/post-transformation strategies. Toward more sustainable one-pot diversity-oriented synthesis of complex nitrogen heterocycles.

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Rapid, versatile, and efficient mechanochemical one-pot processes were developed for the synthesis of 1,5-disubstituted tetrazoles (1,5-Ds-Ts) and complex analogs, such as *bis*-heterocycles (BHCs) and polyheterocycles (PHCs), via multicomponent strategies based on the Ugi-azide four-component reaction (UA-4CR) at room temperature under solvent-free or solvent-less conditions. Furthermore, mechanochemical one-pot diversity-oriented synthesis (DOS) was achieved by coupling UA-4CR with post-transformation processes, such as copper-catalyzed alkyne-azide cycloaddition (CuAAC) and 1,5-pseudoelectrocyclization, thereby increasing molecular complexity and diversity of the products.

Heterocyclic compounds contain one or more rings with at least one heteroatom (nitrogen, oxygen, or sulfur). Among them, nitrogen heterocycles are the main class due to their presence in natural products and their broad biological properties, with applications in pharmaceuticals, agrochemistry, material science, etc.[1] The combination of heterocyclic units enhances the properties of *bis*-heterocycles (BHCs) or polyheterocycles (PHCs) through synergistic effects, thereby improving biological properties compared to the single heterocyclic components.[2] In particular, the incorporation of heterocyclic amide bond bioisosteres, such as 1,5-Ds-Ts and 1,2,3-triazoles, into drug scaffolds is of great interest because they enhance pharmacokinetic and pharmacodynamic properties (Figure 1).[3]

One-pot processes are consecutive, domino, or tandem transformations conducted within a single vessel and play a key role in the design and development of sustainable synthetic strategies to access high-value molecules across both academic and industrial fields. Their advantages over conventional multistep synthesis include lower production costs, reduced environmental impact, avoidance of intermediates purification, and improved overall yields.[4] Isocyanide-based multicomponent reactions (IMCRs) stand out as exceptionally efficient and versatile tools for the green synthesis of nitrogen heterocycles. IMCRs-based one-pot strategies offer additional advantages, including high convergence, atom- and step-economy, mild conditions, broad scope, operational simplicity, high overall yields, and use of readily accessible starting materials.[5]

The incorporation of orthogonal reagents—defined as those having multiple functional groups with distinct reactivity that can be selectively addressed under specific conditions without affecting the others—[6a-b] into IMCRs-based strategies provides access to synthetic platforms useful for further transformations.[6c] It is highlighted that their application toward the one-pot DOS represents one of the most promising areas of research for designing and synthesizing libraries of target molecules with potential applications in various fields. Due to the current environmental challenges, synthetic chemists aim to develop scaffold diversity.[7]

Green technologies, such as alternative energy sources (AES), and their integration into IMCR-based one-pot strategies, are emerging as highly efficient approaches that align with several principles of green chemistry.[8] Among AES techniques, mechanochemistry is considered one of the most promising. It employs mechanical energy induced by impact, shear, or friction forces to promote chemical reactions under solvent-free conditions. Mechanochemistry provides faster reaction kinetics by increasing reactant concentrations, overcoming solubility limitations, and often altering reaction selectivity. Consequently, enables the development of novel, greener synthetic strategies.[9]

Despite its attractive features for eco-friendly synthesis, mechanochemical-IMCR has been little explored; the first report was published by Maleki in 2014 via Groebke-Blackburn-Bienaymé three-component reaction (GBB-3CR).[10] Subsequently, Ugi four-component reaction (Ugi-4CR),[11] and Passerini three-component reaction.[11d,12] Our research group is a pioneer in the design and development of novel greener AES-assisted one-pot strategies via IMCR and IMCR/post-transformations, including ultrasound irradiation (USI)[13] and mechanochemistry,[11c,14] to access nitrogen-heterocyclic target molecules, in good to excellent overall yields.

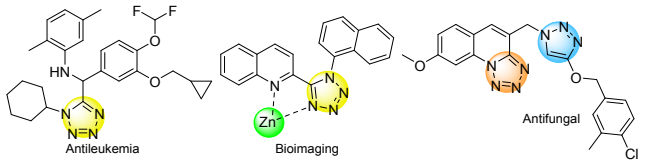

Figure 1. Applications of 1,5-Ds-Ts, tetrazolo[1,5-*a*]quinolines, 1,2,3-triazoles.

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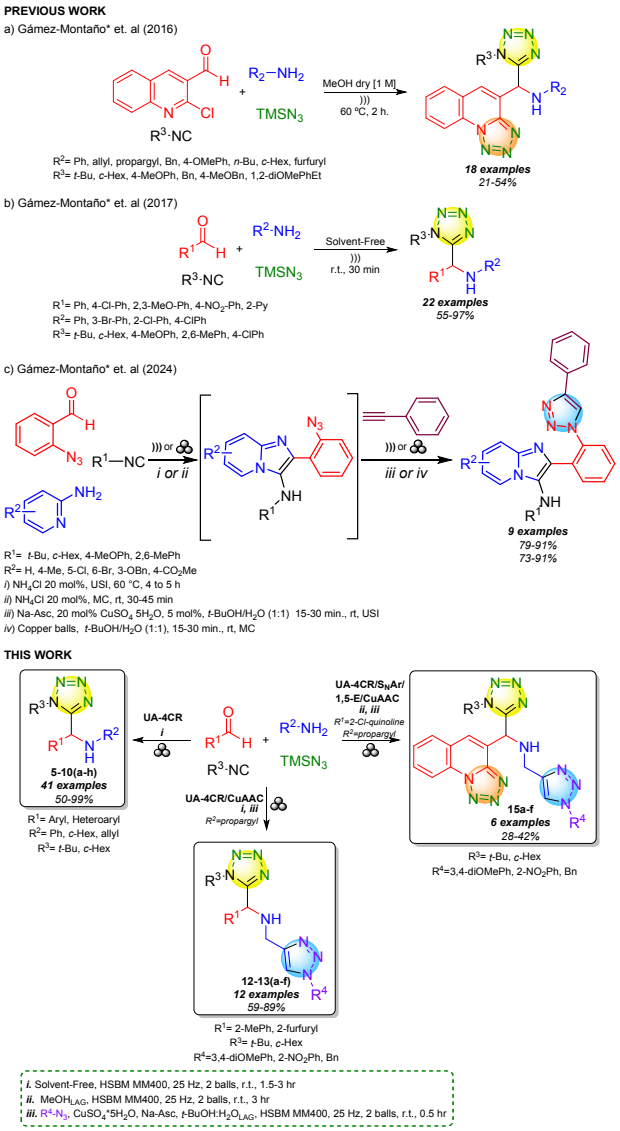
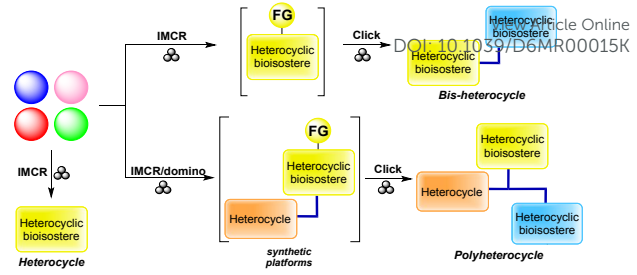
Remarkably, AES-assisted IMCR-based one-pot synthesis of BHCs, including 1,5-Ds-Ts, has been scarcely reported.[15] In particular, the first sonochemical DOS of peptidomimetic nitrogen-heterocycles via IMCR/post-transformation one-pot strategy was reported in 2016.[13b] The first mechanochemical one-pot DOS of heterocyclic peptidomimetics via Ugi-4CR/S_N2 and Ugi-4CR/aldol-type cyclization was reported in 2022.[11c] Additionally, the first mechanochemical one-pot synthesis of BHCs via the GBB-3CR/CuAAC strategy was reported (Scheme 1).[14] To date, the mechanochemical synthesis of tetrazoles via Ugi-azide four-component reaction (UA-4CR), either alone or coupled with post-transformations in one-pot or multistep fashion, has not been reported.

Furthermore, the efficient AES-assisted IMCR-based one-pot synthesis of PHCs drug scaffolds under mild, sustainable conditions remains unreported and represents a significant challenge for modern synthetic organic chemists. IMCR-based one-pot strategies for the synthesis of PHCs are relatively unexplored.[16] To date, none of these approaches have incorporated environmentally benign AES.



Scheme 1. Previous and present work on the DOS of 1,5-DS-Ts analogs via mechanochemical UA-4CR-based strategies.



Scheme 2. Green mechanochemical IMCR and IMCR/post-transformation one-pot strategies: toward DOS of complex nitrogen-heterocycles.

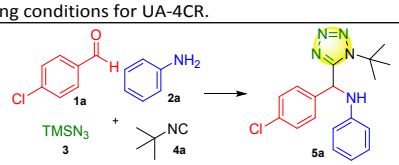
As part of our research program focused on the design and development of greener IMCR-based one-pot strategies, we herein describe the first mechanochemical one-pot UA-4CR and UA-4CR/post-transformation strategies for the DOS of complex nitrogen-heterocycles containing one, two, or three rings, such as 1,5-Ds-Ts, 1,2,3-triazolyl-1,5-Ds-Ts, 1,5-tetrazolyl-tetrazolo[1,5-*a*]quinolines, and 1,5-tetrazolyl-1,2,3-triazolyl-tetrazolo[1,5-*a*]quinolines (Scheme 2).

Results and Discussion

Initially, UA-4CR conditions were optimized using 4-chlorobenzaldehyde (**1a**), aniline (**2a**), $TMSN_3$ (**3**), and *t*-butyl isocyanide (**4a**) to access 1,5-Ds-T (**5a**) (Table 1). Under stirring conditions in MeOH, product **5a** was isolated in 63% yield after 12 hours (entry 1). To develop a greener method, water was tested. Unfortunately, product **5a** was isolated in 35% yield (entry 2), due to the poor solubility of the reactants. Similarly, under solvent-free conditions, the yield decreased further to 22% (entry 3).

Liquid-assisted grinding (LAG), in which a small amount of liquid is added to the reaction mixture to enhance component interaction,[17] was tested using a Retsch Mixer Mill MM400 with either H_2O (entry 4) or MeOH (entry 5), yielding product **5a** in 57% and 87%, respectively. Unfortunately, increasing the number of milling balls (entries 6 and 7) resulted in low yields. In agreement with mechanochemical principles, solvent-free conditions enabled the complete consumption of the starting material within 90 minutes, affording the UA **5a** product in 98% yield (entry 8). Mechanochemistry operates at low frequencies (≈25 Hz) to break bonds and generally requires longer reaction times.[18]

Table 1. Screening conditions for UA-4CR.



Entry[a]	Solvent	Time(h)	Yield (%)[b]
1	MeOH[c,d]	12	63
2	H_2O[c,d]	12	35
3	---[c]	12	22
4	H_2O[e,f]	1.5	57
5	MeOH[e,f]	1.5	87
6	MeOH[g,e]	1.5	70
7	---[g]	1.5	75
8	**---[e]**	**1.5**	**98**

[a]Equimolar quantities (0.213 mmol) of **1a**, **2a**, **3** and **4a** at 25 °C (rt). [b]Yield of isolated product. [c]Stirring conditions. [d][1.0 M]. [e]2 stainless steel balls (*d* = 5 mm), HSBM MM400 (25 Hz). [f]LAG (η = 0.5). [g]4 stainless steel balls (*d* = 5 mm) HSBM MM400 (25 Hz).

The versatility of the mechanochemical UA-4CR strategy under optimized conditions was applied to synthesize 1,5-Ds-Ts (**5-10a-h**, Table 2). The mechanochemical UA-4CR exhibited excellent efficiency, particularly with heteroaryl aldehydes, such as furfural, 2-pyridinecarboxaldehyde, and 2-chloroquinoline-3-carbaldehyde, affording the corresponding products **8a-g**, **9a-f**, and **10a-g** in good to excellent overall yields. It is noteworthy that the versatility of UA-4CR has rarely been reported employing heteroaryl aldehydes and aliphatic amines.[13a,19] On the other hand, aniline displayed high reactivity toward a wide range of aldehydes, providing products in yields ranging from 70-99%. Surprisingly, aliphatic amines such as cyclohexylamine and allylamine afforded moderate to excellent overall yields.

The developed mechanochemical UA-4CR strategy significantly surpasses all previously reported UA-4CR strategies, providing a new IMCR-based one-pot and DOS one-pot strategies, a broader substrate scope, higher overall yields, and improved molecular complexity and diversity. All synthesized compounds were characterized by spectroscopic methods (^{1}H and ^{13}C NMR, IR, and HRMS). Additionally, an adequate crystal for X-ray diffraction analysis (CCDC, see the SI for further details) was obtained to confirm the structure of the 1,5-DS-T **10f** (Figure 2).

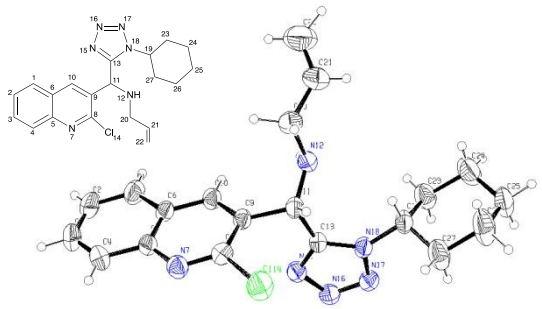
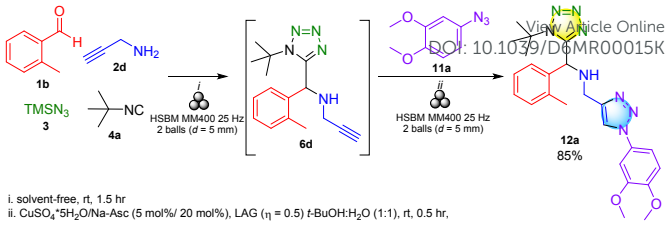


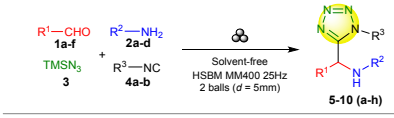
Figure 2. ORTEP molecular structure of **10f** with ellipsoids at 35% probability level.

Complex alkynes generated *in situ* via the optimized mechanochemical UA-4CR strategy were used as a synthetic platform to study the CuAAC reaction. To our knowledge, the AES-assisted CuAAC reaction as a post-transformation for IMCR-based strategies has been reported exclusively by our research group.[13d,14] Encouraged by these results, the mechanochemistry-assisted CuAAC conditions were tested stepwise using alkyne **6d** with 4-azido-1,2-dimethoxybenzene (**11a**), to synthesize triazole **12a**, employing $CuSO_4{\cdot}5H_2O$ with sodium ascorbate, and LAG (η= 0.5) of *t*-BuOH:H_2O.[20] A 90% yield was calculated after 30 min of reaction. Subsequently, the mechanochemical one-pot UA-4CR/CuAAC strategy was tested to synthesize BHC **12a** (Scheme 3). Two heterocycles were constructed with excellent overall yield in 1.5 hr.



Scheme 3. One-pot process by the mechanochemical UA-4CR/CuAAC strategy.

Table 2. Substrate scope mechanochemical UA-4CR[a]



5a R^2 = Ph, R^3 = *t*-Bu (99%)
5b R^2 = *c*-Hex, R^3 = *t*-Bu (56%)
5c R^2 = allyl, R^3 = *t*-Bu (85%)
5d R^2 = Ph, R^3 = *c*-Hex (99%)
5e R^2 = *c*-Hex, R^3 = *c*-Hex (71%)
5f R^2 = allyl, R^3 = *c*-Hex (87%)

6a R^2 = Ph, R^3 = *t*-Bu (79%)
6b R^2 = *c*-Hex, R^3 = *t*-Bu (91%)
6c R^2 = allyl, R^3 = *t*-Bu (88%)
6d R^2 = propargyl, R^3 = *t*-Bu (86%)
6e R^2 = Ph, R^3 = *c*-Hex (86%)
6f R^2 = *c*-Hex, R^3 = *c*-Hex (95%)
6g R^2 = allyl, R^3 = *c*-Hex (93%)
6h R^2 = propargyl, R^3 = *c*-Hex (91%)

7a R^2 = Ph, R^3 = *t*-Bu (99%)
7b R^2 = *c*-Hex, R^3 = *t*-Bu (73%)
7c R^2 = allyl, R^3 = *t*-Bu (86%)
7d R^2 = Ph, R^3 = *c*-Hex (77%)
7e R^2 = *c*-Hex, R^3 = *c*-Hex (72%)
7f R^2 = allyl, R^3 = *c*-Hex (95%)

8a R^2 = Ph, R^3 = *t*-Bu (99%)
8b R^2 = *c*-Hex, R^3 = *t*-Bu (86%)
8c R^2 = allyl, R^3 = *t*-Bu (52%)
8d R^2 = propargyl, R^3 = *t*-Bu (79%)
8e R^2 = Ph, R^3 = *c*-Hex (99%)
8f R^2 = *c*-Hex, R^3 = *c*-Hex (81%)
8g R^2 = allyl, R^3 = *c*-Hex (84%)
8h R^2 = propargyl, R^3 = *c*-Hex (83%)

9a R^2 = Ph, R^3 = *t*-Bu (95%)
9b R^2 = *c*-Hex, R^3 = *t*-Bu (99%)
9c R^2 = allyl, R^3 = *t*-Bu (82%)
9d R^2 = Ph, R^3 = *c*-Hex (99%)
9e R^2 = *c*-Hex, R^3 = *c*-Hex (99%)
9f R^2 = allyl, R^3 = *c*-Hex (86%)

10a R^2 = Ph, R^3 = *t*-Bu (70%)
10b R^2 = *c*-Hex, R^3 = *t*-Bu (62%)
10c R^2 = allyl, R^3 = *t*-Bu (71%)
10d R^2 = Ph, R^3 = *c*-Hex (50%)
10e R^2 = *c*-Hex, R^3 = *c*-Hex (75%)
10f R^2 = allyl, R^3 = *c*-Hex (66%)
10g R^2 = propargyl, R^3 = *c*-Hex (60%)

[a]Reaction conditions: quantities of **1b-f** (1eq), **2a-d** (1eq), **3** (1eq) and **4a-b** (1eq), at rt. **Note:** The scale for each compound is specified in the SI.

Under optimized conditions for the mechanochemical UA-4CR/CuAAC strategy, a series of BHCs (**12a-f** and **13a-f**) were synthesized in good to excellent overall yields (59-89%) using aliphatic and aromatic organic azides (Table 3).

Table 3. Substrate scope mechanochemical one-pot UA-4CR/CuAAC strategy [a]

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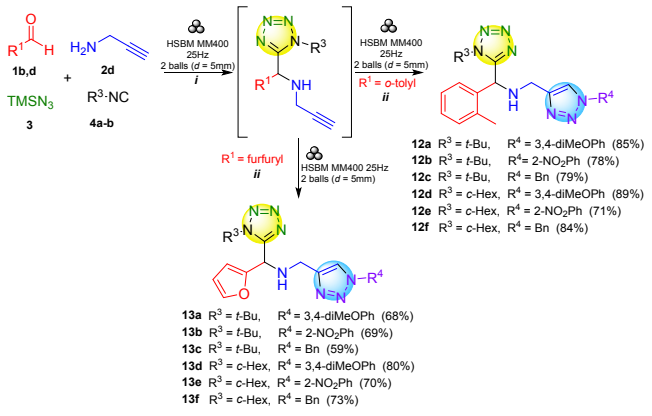
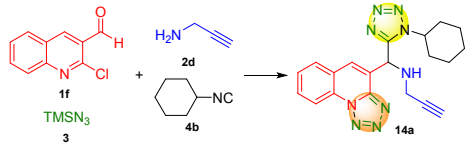


[a]Reaction conditions: Equimolar quantities (0.260 mmol) of **1b,d** (1eq), **2d** (1eq), **3** (1eq) and **4a-b** (1eq), **11a-c** (1eq), rt.

The orthogonal heterocyclic reagent, 2-chloroquinoline-3-carbaldehyde, was selected for its commercial availability, high stability, and synthetic accessibility. It has been reported to synthesize tetrazolo[1,5-*a*]quinoline analogs;[13b,21] however, none of these have been studied on mechanochemistry. Optimization of the one-pot UA-4CR/S_NAr/1,5-pseudoelectrocyclization process initiated with the synthesis of product **14a** using 2-chloroquinolin-3-carbaldehyde (**1f**), propargylamine (**2d**), cyclohexyl isocyanide (**4b**), and $TMSN_3$ (**3**) (Table 4). Under conventional stirring conditions (entry 1), the reaction in MeOH at room temperature afforded an 18% yield. Increasing the temperature to 60 °C resulted in a higher yield and a shorter reaction time (entry 2), leading to tetrazole (thermodynamic product).[22]

The solvent-free mechanochemical conditions were applied for the UA-4CR/S_NAr/1,5-pseudoelectrocyclization; however, the yield was low (entry 3). The addition of LAG (η = 0.5) as H_2O, EtOH, or MeOH (entries 4-6) enhances reagent interaction and stabilizes tetrazole formation through solvation and hydrogen bonding, thereby increasing the overall yield.[22] An increase in the number of milling balls (entry 7) had a detrimental impact on the process.

Table 4. Screening conditions UA-4CR/S_NAr/1,5-pseudoelectrocyclization[a]

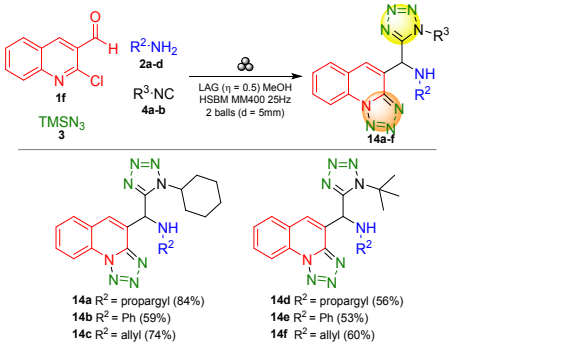


Entry	Solvent (LAG)	Time(h)	Yield (%)[b]
1	MeOH[c]	12	18
2	MeOH[c,d]	6	25
3	----[e]	3	36
4	H_2O[e,f]	4	48
5	EtOH[e,f]	2	53
6	**MeOH[e,f]**	**3**	**84**
7	MeOH[g,f]	3	32

[a]Reaction conditions: quantities of **1f** (0.104 mmol), **2d** (0.104 mmol), **3** (0.241 mmol), and **4b** (0.104 mmol). [b]Yield of isolated product. [c]Stirring conditions [1.0 M]. [d]60 °C. [e]2 stainless steel balls (*d* = 5 mm), HSBM MM400 (25 Hz). [f]LAG (η = 0.5). [g]4 stainless steel balls (*d* = 5 mm) HSBM MM400 (25 Hz).

A series of 3-triazolyl-tetrazolo[1,5-*a*]quinolines (**14a-g**) was synthesized (Table 5). In contrast to previous work,[13b] the current approach enables the first mechanochemical one-pot double-domino process including UA-4CR followed by an S_NAr/1,5-pseudoelectrocyclization for the synthesis of BHCs at room temperature, affording good overall yields without isolating intermediates or changing conditions. It is highlighted that a domino reaction is a one-pot process involving two or more sequential bond-forming transformations that take place under the same reaction conditions, where each step is triggered by functionality generated in the previous one, without requiring intermediate isolations or changes in reaction conditions.[4a]

Table 5. Substrate scope mechanochemical one-pot UA-4CR/S_NAr/1,5-pseudoelectrocyclization strategy[a]

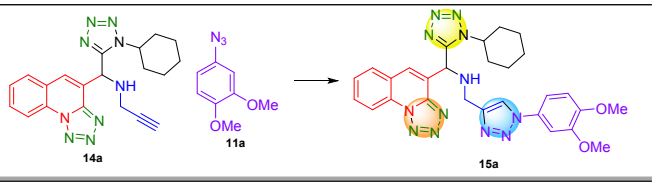


[a]Reaction conditions: quantities of **1f** (0.104 mmol), **2a-d** (0.104 mmol), **3** (0.241 mmol) and **4a-b** (0.104 mmol), rt.

For the synthesis of PHCs, complex alkyne **14a** was employed as a synthetic platform for the CuAAC reaction (Table 5), taking advantage of the reported synergy between CuAAC and mechanochemistry.[23] We calculated good overall yields using a Retsch Mixer Mill MM400 ball mill under solvent-free conditions with CuI as the catalyst (entry 1). Using the catalytic system $CuSO_4{\cdot}5H_2O$ with sodium ascorbate (Na-Asc) (entry 2), afforded a higher yield. The catalytic system offered additional advantages, such as tolerance to aqueous media, lower cost, and shorter reaction times.[20]

Next, the effect of LAG in the reaction was tested, demonstrating a positive impact on the CuAAC under classical catalytic conditions (entries 3 and 4). MeOH as a LAG significantly decreased the overall yield. In contrast, the *t*-BuOH:H_2O mixture as LAG improved reaction efficiency by integrating the components and stabilizing Cu(I).[20]

Table 6. Screening conditions for CuAAC[a]

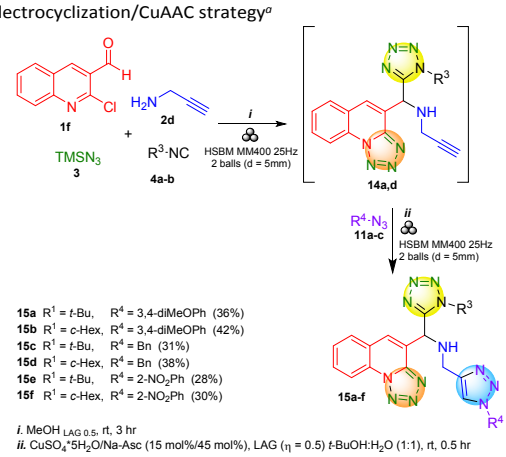


Entry	Solvent	Catalyst	Time(h)	Yield (%)[b]
1	----	CuI[e]	1.5	40
2	----	$CuSO_4$/Na-Asc[f]	1.5	59
3	MeOH[c]	$CuSO_4$/Na-Asc[f]	1	34
4	***t*-BuOH:H_2O**[c,d]	**$CuSO_4$/Na-Asc**[f]	**0.5**	**88**

[a]Reaction conditions: equimolar quantities of **14a** (0.104 mmol) and **11a** (0.104 mmol) at rt, 2 stainless steel balls (*d* = 5 mm), HSBM MM400 (25 Hz). [b]Yield of isolated product. [c]LAG (η = 0.5). [d]1:1 *v/v*. [e]10 mol%. [f]15 mol%/45 mol%.

Products **15a-f** were synthesized in one-pot via the mechanochemical UA-4CR/S_NAr/1,5-pseudoelectrocyclization/CuAAC (Table 7). Exploring the scope with aliphatic and aromatic organic azides afforded compounds **15a-f** in moderate to good overall yields (28-42%). Notably, three rings were constructed in only 3.5 hours of total reaction time. A plausible reaction mechanism for the one-pot strategy is provided in the SI.

Table 7. Substrate scope mechanochemical one-pot UA-4CR/S_NAr/1,5-pseudoelectrocyclization/CuAAC strategy[a]



[a]Reaction conditions: quantities of **1f** (0.104 mmol), **2d** (0.104 mmol), **3** (0.241 mmol) and **4a-b** (0.104 mmol), **11a-c** (0.104 mmol).

Mechanochemical reactions involving nitrogen-rich compounds such as azides and tetrazoles require safety considerations due to their substitution-dependent energetic properties, with substituted derivatives generally exhibiting lower sensitivity than low-molecular-weight or inorganic analogues.[24] In the present study, reactions were conducted on small scale, avoiding significant increases in temperature and pressure using short milling times and non-low-molecular-weight components, and no evidence of uncontrolled exothermic behaviour or pressure build-up was observed. Nevertheless, the scale-up of reactions should be preceded by appropriate hazard assessment and incremental scaling protocols.[25]

Developing metrics to quantify the sustainability of chemical practices is crucial for validation and advancing green chemistry.[26] Green metrics, such as Atom Economy (AE), Atom Efficiency, *E*-factor, Reaction Mass Efficiency (RME), Process Mass Intensity (PMI), and Carbon Efficiency (CE), were calculated for the representative products obtained from the mechanochemical UA-4CR and UA-4CR/post-transformation strategies. The calculated metrics support the greenness and overall sustainability of the developed approach (Table 8).

Table 8. Comparison of the calculated green metrics with the ideal values.

		Compound					
Green metrics	**Ideal**	**5a**	**6d**	**8a**	**12a**	**14a**	**15a**
AE (%)	**100**	79.1	75.9	76.7	83.7	62.4	70.8
Atom efficiency (%)	**100**	78.1	65.4	76.0	71.0	52.5	29.5
***E*-factor**	**0**	0.3	0.5	0.3	0.8	1.1	3.8
RME (%)	**100**	78.1	65.4	76.0	71.0	52.5	29.5
PMI	**1**	1.3	1.5	1.3	1.8	2.1	4.8
CE (%)	**100**	84.6	72.6	83.4	75.4	62.5	33.5

Note: Detailed calculations for each compound are provided in the SI.

Conclusions

This work provides unprecedented contributions to the fields of mechanochemistry, IMCR-based one-pot processes, and DOS. Novel green multicomponent strategies integrating highly efficient tools, such as domino process and click reactions, were developed for the sustainable synthesis of nitrogen-heterocycles, including BHCs and PHCs.

Furthermore, efficient mechanochemical UA-4CR and UA-4CR/post-transformation strategies were developed for the synthesis of 1,5-Ds-Ts and their structurally complex analogs, affording moderate to excellent overall yields consistent with the number of assembled rings in the one-pot process. These compounds incorporate well-known amide bond bioisosteres in medicinal chemistry, such as 1,5-Ds-Ts and 1,4-disubstituted 1,2,3-triazoles.

The synergy of powerful synthetic tools, such as IMCR, pseudopericyclic, and click reactions, significantly enhances molecular diversity and complexity, enabling the synthesis of nitrogen PHCs. Mechanochemical-IMCR strategies have strong potential as greener synthetic methodologies of choice in modern organic synthesis, offering notable advantages, including solvent-free or solvent-less conditions, faster reaction kinetics due to higher reactant concentrations, overcoming solubility limitations, reduced toxicity and pollution, lower energy consumption and operational costs, and improved overall yields. Furthermore, IMCR is one of the most powerful synthetic tools for developing greener strategies, as it inherently incorporates many of the principles of green chemistry.

Author Contributions

A. C.-D. Investigation, Methodology, Writing -original draft, Writing-review & editing, D. G.-G., Investigation, Methodology, Writing -original draft, Writing-review & editing, S. C. R.-L. Investigation, Methodology, Writing -original draft, and R. G. M. supervision, resources, Writing-review & editing. A. C.-D. and D. G.-G. contributed

equally to this work. All authors discussed the results and commented on the manuscript. All authors agree to be held accountable for the content therein.

Conflicts of interest

There are no conflicts to declare.

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.