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Isocyanide based multicomponent click reaction: Green and an improved synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles

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An improved ultrasound assisted green synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles via novel isocyanide based multicomponent click reaction (IMCCR) under mild, solvent, catalyst and column-free conditions have been developed. This new, green and sustainable IMCCR methodology resulted in good to excellent yields (71-97%) in shorter reaction times.

Isocyanide based multicomponent reactions (IMCRs) have been widely known as useful tool toward a facile synthesis and functionalization of diverse nitrogen heterocycles.¹ Despite this, the design and development of more green and eco-friendly IMCRs for the synthesis of nitrogen heterocycles is an unexplored field. Water, one of the cheapest and abundant source of green-nucleophile has been rarely used as a component in IMCR to synthesize heterocycles. To our knowledge, three IMCR methodologies are known, among which two methods² need palladium catalysts and heating conditions, while third method³ describes the use of ten times excess isocyanide in non-eco-friendly solvent with very limited substrate scope. However, mild and green IMCRs using water as a component towards the synthesis of nitrogen heterocycles or polyheterocycles has not yet been reported.

IMCRs and click reactions shares various common features and often considered as ideal reactions. The concept of click chemistry is mainly focused on the construction of carbon-heteroatom bonds using spring-loaded reactants under mild reaction conditions. Click reaction must fulfill a set of stringent criteria, particularly, starting materials should be easily available, reaction proceed under mild neat conditions or in green solvents, forms non-harmful by-products, purification should be non-chromatographic and provide high yields.⁴ In this context, 1,3-dipolar cycloaddition offers a convenient and straightforward approach to synthesis of a wide range of five-

membered ring nitrogen heterocycles. Among them, [3 + 2] cycloaddition has attracted great interest due to its status as the best Click reaction to date.⁵

From the green chemistry point of view, the development of green, solvent and catalyst-free IMCRs under mild conditions is a hot topic in organic synthesis. In this context, the Ultrasound irradiation (USI), a convenient energy source with several advantages, which produces the formation, growth and implosive collapsing bubbles, as a result strong shock waves are generated which causes high velocity collisions between reactants.⁶ These collisions creates great heating, leading to the melting of reactants particularly in solvent-free reactions and forms expected products in short times with minimal by-products.⁷ Also, in recent years solvent-free multicomponent reactions have gained great importance in organic synthesis.⁸ In spite of this, the synthesis of heterocycles via IMCRs strategies or methodologies based on mild, catalyst and solvent-free are still infrequent.⁹

The 1-substituted tetrazoles (1-ST's) have attracted much attention because of their various applications, mainly in field of medicinal and coordination chemistry. For instance, compound **1** is anti-inflammatory active,^{10a} **2** is anticoagulant,^{10b} **3** is strong phytocidal active^{10c} and **4** used as aluminum^{10d} and copper^{10e} corrosion inhibitor. Additionally, compound **5** is an antibacterial and antitumor agent^{10f} and **6** is a coordination polymer ligand (fig. 1).^{10g}

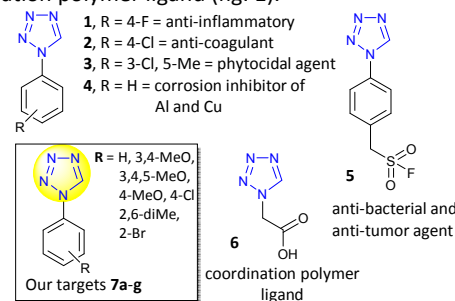


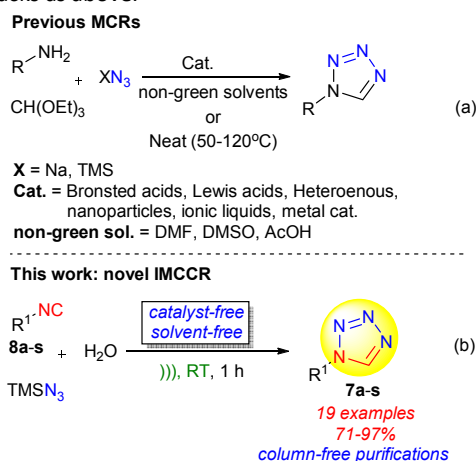
Figure 1. Target compounds and some applications of 1-ST molecules.

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The synthesis of 1-ST's from isocyanide has been less explored, though first method was reported in 1910 using large excess amounts of hydrazoic acid (HN₃).¹¹ However, HN₃ is very toxic and harmful compound and its excess content in reaction can lead to violent explosions.¹² Further, in 2004 Yamamoto et al. reported methodology utilizing trimethylsilyl azide (TMSN₃) instead of toxic HN₃ to afford 1-ST's, under catalytic conditions at 60 °C.¹³ Few more methodologies known in literature wherein cat. HCl,^{14a,14b} ZnBr₂^{14c} and supramolecular self-assembled catalyst^{14d} were used to synthesize 1-ST's from isocyanide and TMSN₃. However, in these protocols, scope of the reaction is narrow, long reaction times and catalysts were must require with high temperature conditions. Recently, Dömling et al. reported the catalyst-free [3 + 2] cycloaddition (two-component reaction) between isocyanoacetamides and TMSN₃ in MeOH: H₂O solvent system to synthesize 1H-tetrazolyl acetamides.¹⁵ However, the scope of the reaction was not studied extensively as this method is limited to only for *N*-alkyl isocyanoacetamides. Additionally, longer reaction times (20 hrs), non-commercial isocyanides and workup procedures limits the synthetic applications of this methodology.

The most common strategy for the synthesis of 1-ST's is the multicomponent reaction (MCR) of primary amines, triethyl orthoformate and sodium azide, always achieved by using catalyst (Scheme 1a),¹⁶ which suffers from various disadvantages such as high temperature, non-green solvents, long reaction times, expensive reagents, use of hazardous NaN₃ and toxic catalysts make these methods non-green and limited. Besides, this MCR strategy was also reported under solvent-free¹⁷ and USI assisted¹⁸ conditions with the same drawbacks as above.



Scheme 1. Previously reported MCR methodologies vs IMCCR strategy towards 1-ST's.

However, despite these all reports mentioned above, an IMCR toward a 1-ST's has never been reported. Accordingly, it is essential to develop a versatile, efficient and operationally simple IMCR methodology to improve the synthesis of 1-ST's from using isocyanides and TMSN₃. To the best of our knowledge, no IMCR and no mild, green and catalyst-free MCR via click [3 + 2] cycloaddition has been reported for the synthesis of 1-ST's.

As a part of our ongoing research programme towards green strategies based on IMCRs to synthesize tetrazoles,¹⁹ we recently reported the solvent and catalyst-free endogenous water triggered synthesis of 1,5-disubstituted tetrazoles under USI by Ugi-azide IMCR,²⁰ where HN₃ was generated *in situ* via reaction between TMSN₃ and H₂O formed during aldehyde-amine condensation and confirmed by mass experiment. A query arose, since the H₂O could be used as proton source to generate HN₃ from TMSN₃, if an isocyanide is treated with TMSN₃ in the presence of H₂O under USI: Will it form the expected 1-ST product via formal [3 + 2] cycloaddition? (Scheme 1b). Herein, we report improved ultrasound assisted synthesis of 1-ST's via novel, green, solvent, catalyst and column-free isocyanide based multicomponent click reaction (IMCCR) and a complementary strategy to synthesize 1-ST's.

To confirm this hypothesis, we started our studies with the cycloaddition of 4-methoxyphenyl isocyanide **8a** with TMSN₃ and H₂O as a model reaction under catalyst and solvent-free USI conditions. Our hypothesis was found to be correct, leading to the formation of 1-(4-methoxyphenyl)-1H-tetrazole **7a** in 42% yield (Table 1, entry 1). For the same reaction, there was little increase in yield after 4 hours (Table 1, entry 2). When the equivalents of TMSN₃ and H₂O were increased, 67% yield of expected product **7a** was isolated (Table 1, entry 3). Further, increased equivalents of TMSN₃ and H₂O (2 equiv. each) gave product **7a** in an excellent yield of 94% even in a shorter reaction time (Table 1, entry 4).

However, comparable yield was obtained when the similar reaction carried out under stirring condition at RT without USI (Table 1, entry 5). The reaction time was increased approximately three-fold compared with previous reaction performed under USI conditions. Thus, reaction accelerated under USI conditions giving higher yields compared to the RT conditions (Table 1, entries 4 and 5). Finally, we identified the following protocol as optimal: When **8a** (1 equiv.) reacted with TMSN₃ and H₂O (2 equiv. each) under solvent and catalyst-free USI conditions for 1 hour, the desired tetrazole **7a** was isolated in 94% yield (Table 1, entry 4).

With the optimized reaction conditions, we explored the **Table 1.** Screening conditions.

entry	equiv.		time (h)	yield (%) ^a
	TMSN ₃	H ₂ O		
1	1	1	2	42
2	1	1	4	48
3	1.5	1.5	2	67
4	2	2	1	94
5 ^b	2	2	3	90

^aisolated product. ^breaction without USI, on stirring at RT.

scope of the IMCCR with a variety of isocyanides to synthesize 1-ST analogues **7a-s** (Table 2). Gratifyingly, less nucleophilic aromatic isocyanides gave corresponding 1-ST's in excellent yields **7a-c**. Interestingly, sterically hindered and low-nucleophilic *ortho* dimethyl substituted phenyl isocyanide afforded a good yield of desired product **7d** with a slight prolonged reaction time, further expanding the scope of this protocol. The reactions of *halo* aryl isocyanides also produced corresponding tetrazole products **7e-f** in high yields, demonstrating the versatility of the developed novel IMCCR. The unstable and rarely used phenyl isocyanide underwent smooth conversion to afford 1-ST **7g** in a good yield of 81%.

The feasibility of this IMCCR was then examined with differently substituted benzyl and phenethyl isocyanides. Notably, benzyl, phenethyl and their various *methoxy* substituted analogues were well tolerated, furnishing the desired products **7h-p** in excellent yields. Furthermore, the reaction is not limited to only aromatic, benzyl or phenethyl isocyanides, but also aliphatic isocyanide worked well, leading to expected 1-ST **7q** in an excellent yield of 92%. Next, we examined the outcome of this IMCCR with isocyanoacetamides. Interestingly, the reaction under current conditions afforded desired products **7r-s** in good yields, with a slightly prolonged reaction time.

The scalability of this strategy was examined by carrying out gram scale reaction under the optimized conditions and isolated the expected product **7a** in 89% yield (Table 2).

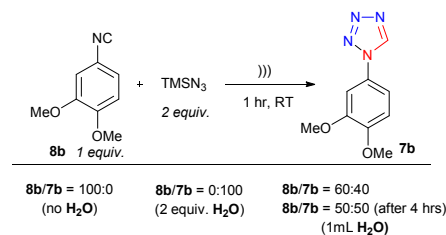
Table 2. Synthesis of 1-ST's **7a-s**^a via IMCCR.

$\text{R}^1\text{-NC} + \text{TMSN}_3 + \text{H}_2\text{O} \xrightarrow[\text{RT, 1 h}]{\text{catalyst-free solvent-free}} \text{R}^1\text{-7}$	
	<p>7a, R = 4-MeO (94%) (89% for 8.2 mmol-scale)</p> <p>7b, R = 3,4-MeO (95%)</p> <p>7c, R = 3,4,5-MeO (88%)</p> <p>7d, R = 2,6-Me (78%)^b</p> <p>7e, R = 4-Cl (78%)</p> <p>7f, R = 2-Br (85%)</p> <p>7g, R = H (81%)</p> <p>7h, R = H (97%)</p> <p>7i, R = 4-MeO (87%)</p> <p>7j, R = 3,4-MeO (90%)</p> <p>7k, R = 2,3-MeO (88%)</p> <p>7l, R = 2-MeO (84%)</p> <p>7m, R = 2,4-MeO (88%)</p> <p>7n, R = H (95%)</p> <p>7o, R = 4-MeO (87%)</p> <p>7p, R = 3-MeO (92%)</p> <p>7q (92%)</p> <p>7r, R = (71%)^b</p> <p>7s, R = (76%)^b</p>

^aThe reactions were carried out using **8** (1 equiv.), TMSN₃ and H₂O (2 equiv. each), ^b reaction time 2 h for **7d**, **7r** and **7s**.

The role of H₂O amount on reaction was investigated using isocyanide **8b** and TMSN₃ as the model (scheme 2). Reaction under the standard conditions without H₂O did not furnish product **7b**. This result implies that H₂O is necessary to generate reactive species HN₃ in reaction, which clearly fills the lack of information in similar previous report.¹⁵ Once the H₂O (2 equiv.) was added to the reaction, single product **7b** was obtained with complete conversion. However, after increasing

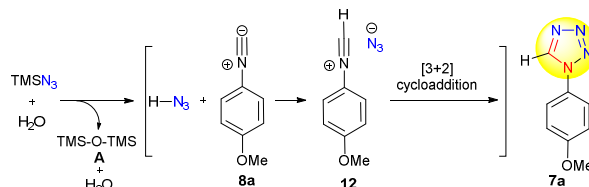
the H₂O amount to 1 mL, the reaction rate decreased significantly and a



Scheme 2. Role of water amount on reaction.

mixture of isocyanide **8b** and product **7b** was obtained at a ratio of 60:40 after 1 hr and 50:50 after 4 hrs, determined by ¹H NMR of crude reaction mixture. This result concludes that only a two-equimolar amount of H₂O is necessary and effective instead of using it in excess as solvent and thereby confirms that the role of H₂O is as a component.

Based on the previous reports,^{13, 21} a plausible mechanism for IMCCR is developed (Scheme 3). Initially, water reacts with TMSN₃ to generate HN₃ and hexamethyldisiloxane **A**.²⁰ Then, the formed HN₃ would protonate isocyanide **8a** to form nitrilium intermediate **12**. This later one undergoes spontaneous formal [3 + 2] cycloaddition with azide ion to afford final product 1-ST **7a**.



Scheme 3. Plausible IMCCR mechanism.

In the previous reports,^{13,14a,14b,21} catalytic amounts of strong acids were used to form key intermediate nitrilium ion **12** (scheme 3) from isocyanide in heating. The role of water in reaction is shown in mechanism (scheme 3) where TMSN₃ and H₂O reacts to give HN₃, the later one plays dual role in reaction. First, due to its acidic nature it protonates the isocyanide to give intermediate **12**, thus avoiding the use of acid catalysts and secondly the liberated azide ion undergoes [3 + 2] cycloaddition with **12** to afford tetrazole product. Moreover, as soon as the HN₃ forms in reaction it rapidly gets reacted, probably due to the following reasons: 1) high spontaneity of [3 + 2] cycloaddition in solvent-free conditions, and 2) reaction rate acceleration in USI conditions, thus avoiding the chances of HN₃ accumulation in reaction.

This novel strategy complies with the requirements of click chemistry,⁴ which are as follows: a) variety of readily available isocyanides reacts easily with in situ generated HN₃ under solvent and catalyst-free room temperature conditions to give 1-STs in high yields, b) as reactions are solvent-free, at the end liquid mixtures formed, which are purified by precipitation (except a few **7g**, **7j**, and **7l**), thus avoiding chromatographic purification and c) while performing reactions, there is no need to take specific precautions as reactants are compatible

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with air or water. Although, Ugi IMCR is considered as multicomponent click reaction due to its significant similar features with click reaction,²² the mild, green and solvent-free IMCR involving click [3 + 2] cycloaddition has not yet been reported. Thus, to the best of our knowledge, this protocol reported here is first mild, green and solvent-free strategy so far of an IMCCR to synthesize heterocycles. Moreover, for this study we used ultrasonic cleaning bath (45 kHz) which is an excellent alternative non-conventional source of energy, with very good sound distribution throughout liquid bath and is inexpensive.

All synthesized compounds were characterized by ¹H, ¹³C, FT-IR and HRMS.

In conclusion, we have developed an efficient USI assisted strategy to improve the synthesis of 1-ST's via novel IMCCR approach involving [3 + 2] cycloaddition. To our knowledge, this is the first protocol for mild and green synthesis of 1-ST's via MCR and first IMCR to do so. Also, this is the first solvent and catalyst-free, mild and green IMCR strategy using water as a component towards heterocycles. It is worthy to mention that, this is first solvent and catalyst-free click via [3 + 2] cycloaddition methodology wherein water generated HN₃ is used. This developed IMCCR strategy has several advantages over the previously reported MCR strategy such as solvent, catalyst and column-free synthesis, short reaction times, mild reaction conditions, high yields, environmental friendliness and operational simplicity. Besides, this strategy should prove useful for the facile synthesis of such 1-ST scaffolds on an industrial scale. It is important to note that present IMCCR methodology completely meet the click and green chemistry criteria.

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Conflicts of interest

There are no conflicts to declare.

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