Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8gc01516c

Received 16th May 2018,
Accepted 11th July 2018

DOI: 10.1039/c8gc01516c

rsc.li/greenchem

Catalyst and solvent free microwave-assisted synthesis of substituted 1,2,3-triazoles†

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We report a microwave-assisted catalyst and solvent free synthesis of 1,2,3-triazoles through the cycloaddition of trimethylsilylazide and acetylenes. Utilization of a thermally stable azide source, elimination of a metal catalyst, solvent or any additives, and a convenient isolation procedure result in an overall greener approach to access 1,2,3-triazoles on a practical scale with good to excellent yields (55–99%).

NH-1,2,3-Triazoles are amongst the most desirable compounds in biomedical research due to their diverse biological properties such as anticancer,[1–5] antifungal,[6–9] antituberculosis,[10–12] and antibacterial activities (Fig. 1).[13–17] Their ability to readily bind with a variety of receptors and enzymes in biological systems has resulted in their extensive application in medicinal chemistry.[18] 1,2,3-Triazoles can be easily accessed through 1,3-dipolar cycloaddition of an azide with acetylene substrates first discovered by Michael in 1893,[19] and further studied by Huisgen as a member of the family of dipolar cycloadditions.[20–22] This class of reactions was classified by Woodward and Hoffmann as thermally allowed pericyclic processes.[23] Later, Sharpless *et al.* categorized such chemistry under click reactions, the term he coined to address "powerful, highly reliable and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links".[24] A copper-catalyzed variation for regioselective 1,4-disubstituted cycloaddition of azides and terminal alkynes was independently discovered by Fokin, Sharpless *et al.*[25] and Meldal *et al.*[26] in 2002. Later, with the discovery of ruthenium-catalyzed cycloaddition of azides and alkynes,[27,28] ready access to all 1,2,3-triazole regioisomers became possible. While click chemistry has been widely used in supramolecular chemistry,[29] catalysis and materials science,[30–32] the pharmaceutical industry gained the most benefits from click chemistry to synthesize drugs and drug-like molecules.[9,33–35] However, for biological applications the potential toxicity of even trace amounts of metal catalyst has always been of great concern.[36] Moreover, the toxic and explosive nature of sodium azide, the commonly used azide source, raises safety concerns, especially for practical scale synthesis. Therefore, there has been increasing interest in employing safer reagents and developing alternative metal free click reactions, such as using other non-metal additives to carry out the click chemistry,[37,38] or employment of highly strained alkynes[39,40] or highly ambident electrophilic alkynes[41,42] to accelerate the reaction rate. However, a scalable metal-free protocol that utilizes safer substrates and produces minimal wastes for the synthesis of 1,2,3-triazoles has not yet been achieved.

We were therefore motivated to develop an alternative green method highly suitable for biological applications, which is solvent-free, metal-catalyst/additive free, and atom economical that utilizes safer reagents. Thus, trimethylsilyl azide ($TMSN_3$), a convenient and thermally safer replacement of sodium azide,[43] was selected as the azide source. Microwave irradiation was preferred for heating the reaction mixtures to elevated temperatures over the conventional heating methods as: (a) microwave-assisted heating has been widely used for synthesis

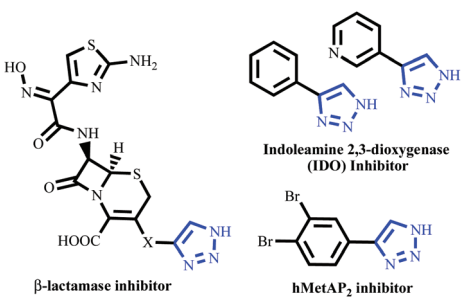

Fig. 1 Few examples of biologically active 1,2,3-triazoles.

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†Electronic supplementary information (ESI) available. CCDC 1843653. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8gc01516c

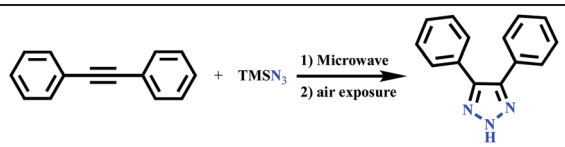
and is compatible with the process-scale preparation of pharmaceutical compounds,[44–46] (b) utilization of microwaves generally reduces side reactions, improves yields, and enhances reproducibility,[45,47] and (c) scientific microwave reactors record key reaction parameters such as microwave power, reaction time, and internal pressure of the reaction vessel throughout the reaction, thus allowing for a deeper understanding of the reaction chemistry. Recently, there has been considerable growth in using microwaves to synthesize 1,2,3-triazoles. However, to the best of our knowledge, none of the microwave procedures are catalyst/additive and solvent free.[48–57]

Optimization was carried out by conducting a series of microwave reactions using diphenylacetylene as a model substrate (Table 1). Initially a 1 : 1 ratio of trimethylsilyl azide and diphenylacetylene was exposed to microwave irradiation at a constant temperature of 200 °C for one hour to obtain *N*-trimethylsilyl 4,5-diphenyl-1,2,3-triazole. Subsequently, exposure of the reaction mixture to air produced NH-4,5-diphenyl-1,2,3-diphenyltriazole (**11**), as traces of moisture readily hydrolyse the trimethylsilyl group to furnish the free N–H group. However, most of the starting materials remained unreacted affording **11** in only 8% yield (entry 1). A higher amount of the triazole product was obtained with increased reaction time (entry 2–4). To our surprise, when the reaction was carried out at lower temperatures, even with a higher quantity of reagents, a drastic decline in the yields was observed, revealing the critical role of heating in this reaction (entries 5–7). Therefore, the optimum temperature of 200 °C was chosen for the rest of the optimization. When the amount of trimethylsilyl azide was increased to 1.5 equivalents (entries 8 and 9) promising improvement was observed in the overall yield; however, the most encouraging result (84% yield) was obtained only after the reaction was given enough time (6 h) to reach an internal vessel pressure of near zero (entry 10). Fig. 2 illustrates the temperature and pressure profiles of the reaction with respect to time at a constant temperature of 200 °C, as recorded using the microwave reactor. Initially, when the reaction mixture is heated up to the desired temperature, an elevation in pressure is observed due to the increase in the vapour pressure of substrates. As the reaction proceeds, a gradual decline in pressure is observed as the final product (triazole) has a lower vapour pressure than that of the reactants. Consequently, the completion of the reaction can be visualized as the appearance of a plateau (or an internal pressure of zero) in the time–pressure profile (for details see the ESI†).

The scope of this method was subsequently investigated by conducting microwave-assisted cycloaddition reactions of different acetylenes (on a 3–5 mmol scale, for details see the ESI†) with trimethylsilyl azide at 200 °C. The progress of the reaction was monitored by the change in the internal pressure of the vessel as discussed earlier. The efficacy of this method was initially tested for terminal alkynes containing aromatic groups (**1**–**7**). To our delight, this method afforded triazoles in excellent yields for both electron-rich (**1**,**2**) and electron-deficient aromatic alkynes (**3**). Moreover, all halogenated substrates were well tolerated under the reaction conditions providing good to high yields of products (**4**–**7**).

Next, an alicyclic substrate (cyclopropylacetylene) was treated with trimethylsilyl azide under the reaction conditions. Excitingly, cyclopropylacetylene also readily participated in the reaction, producing the corresponding triazole (**8**) in an excellent yield (80%), and thus demonstrating the applicability of this method for both aromatic and aliphatic terminal alkynes. Next, various symmetric and asymmetric internal alkynes (**9**–**16**) were subjected to the reaction conditions to explore the effect of polarity and steric hindrance on the overall yield and time of the reactions. Since polar molecules selectively absorb microwave irradiation while nonpolar molecules remain inert to them, the presence of polar moieties is crucial to achieve a more potent heating throughout the reaction. Therefore, as the number of polar moieties increases on the substrates, a

Table 1 Optimization of the reaction conditions[a]



1 equiv. **11**

Entry	$TMSN_3$ (equiv.)	Time (h)	Temperature (°C)	Yield[b] (%)
1	1	1	200	8
2	1	2	200	10
3	1	4	200	41
4	1	8	200	53
5	1.5	3	100	Trace
6	2.5	3	100	Trace
7	2.5	3	150	>5
8	1.5	2	200	27
9	1.5	3	200	40
10	**1.5**	**6**	**200**	**84 (28%)**[c]

[a] Reaction conditions: All reaction vessels were sealed under inert conditions of either nitrogen or argon, and were exposed to air for 30 min after microwave irradiation. [b] Isolated yield after column purification. [c] This reaction was also subjected to conventional heating (oil-bath) and the corresponding triazole was obtained in only 28% yield.

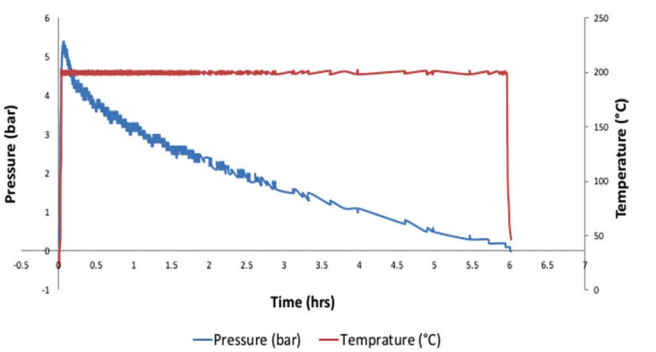


Fig. 2 Data acquired from the microwave reactor for the reaction of diphenylacetylene and trimethylsilyl azide.

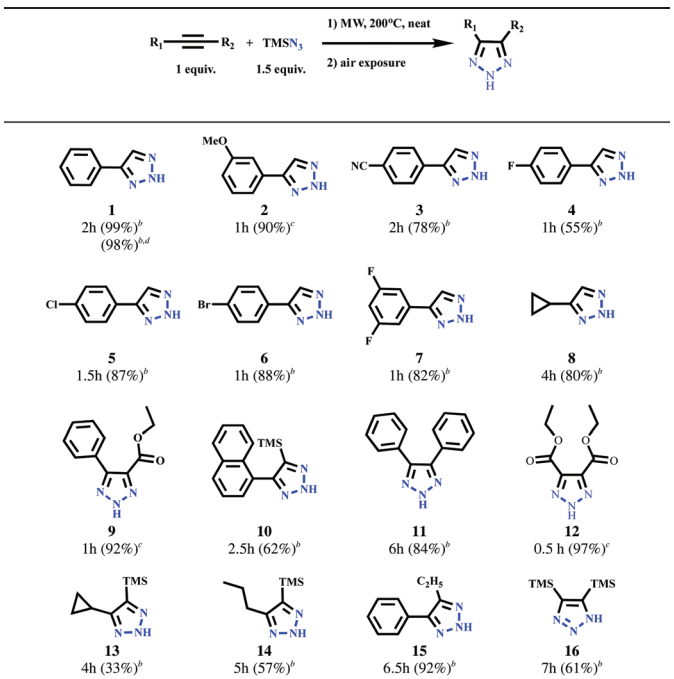
shorter reaction time can be expected. Likewise, as shown in Table 2, a longer reaction time was required for obtaining **9**, which has one polar group when compared to **12** with two polar moieties. However, it is worth noting that the presence of two polar moieties in **12** is not the sole reason for its shorter reaction time. It is well understood that a more electron deficient alkyne undergoes faster 1,3-dipolar cycloadditions; therefore, the effect of two highly electron-withdrawing groups on the rate of the reaction cannot be neglected. Likewise, when **9** and **11** are compared, the replacement of an ethyl carboxylate with a phenyl group results in a drastic increase in the reaction time as both the number of polar moieties and the electronic nature of the molecule have been unfavourably affected.

Furthermore, silylalkynes in general showed a lower reaction rate, as observed from the pressure profile of the reaction, and also afforded an overall lower yield when compared to those without trimethylsilyl groups. For instance cyclopropylacetylene was reacted with $TMSN_3$ to provide compound **8** in an excellent yield of 80% after 4 hours whereas with cyclopropyl(trimethylsilyl)acetylene, the yield of the corresponding triazole (**13**) was significantly less (33%). We believe that the presence of the trimethylsilyl moiety not only interferes with the rate of the reaction due to steric hindrance, but also the β-silicon effect of this moiety generates a more electron rich alkyne, which ultimately is unfavourable for the 1,3-dipolar cycloaddition reactions. Similarly, lower yields of **10**, **14**, and **16** can be explained by both the steric effect and the β-silicon effect of the trimethylsilyl moiety.

It should also be noted that the majority of the isolated triazoles, shown in Table 2, are observed in NMR as the 2*H* tautomers. Although the 1,3 cycloaddition between the alkyne and trimethylsilyl azide initially generates the 1*H* tautomer, the rapid tautomerization results in the 2*H* isomer which is reportedly the more thermodynamically stable tautomer. Interestingly, in the case of **16**, the ^{13}C NMR spectrum showed two different quaternary carbon peaks at 150.6 and 139.8 ppm, and the ^{1}H NMR showed the presence of two trimethylsilyl peaks around 0.38 ppm, revealing the lack of symmetry in the chemical structure of **16**. This was tentatively explained as the result of the exclusive presence of the 1*H* tautomer. Thus, to gain a better understanding of the reaction, we conducted a variable temperature NMR study. The methyl peaks gradually became sharper with decreasing temperature and ultimately appeared as a multiplet at −10 °C. Furthermore, even at a higher temperature of 45 °C, the two distinct trimethylsilyl peaks were still observed, and thus reflecting a very high energy barrier of tautomerization for **16** from the 1*H* to 2*H* tautomer (Fig. 3-left). Indeed, DFT calculations showed that even though the 2*H*-tautomer (**B**) is more stable than **A** by 1.8 kcal mol^{-1}, a high activation energy of 46.3 kcal mol^{-1} prevents the tautomerization of **B** to **A**. However, the high activation energy can be easily circumvented in acidic media through deprotonation–reprotonation to access the more stable tautomer (**16B**), as the addition of a drop of trifluoroacetic acid to a solution of **16** in $CDCl_3$ resulted in the instantaneous formation of **16B** at room temperature (as observed by the appearance of only one quartenary carbon for the triazole ring at 146 ppm).

Additionally, Goddard *et al.*[58] have reported an extensive crystal structure analysis of the 1*H* and 2*H* tautomers of the parent 1,2,3-triazole, where they have successfully distinguished the crystal structure of the tautomers based on the bond angles, as the N atom bearing the H atom shows a larger

Table 2 Reaction of trimethylsilyl azide with various acetylene substrates[a]



[a] Reaction conditions: All reaction vessels were sealed under inert conditions of either nitrogen or argon, and were exposed to air for 30 minutes after microwave irradiation. All reactions were conducted at 3–5 mmol scales. [b] Reported yields are isolated yield after recrystallization (for details see the ESI). [c] Reported yields are isolated yield after flash column chromatography (for details see the ESI). [d] The reported yield is obtained from 12 mmol of phenyl acetylene.

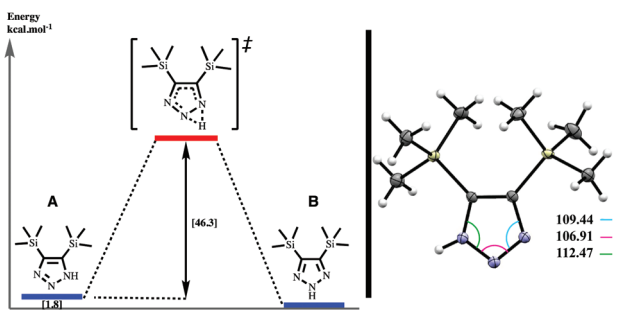
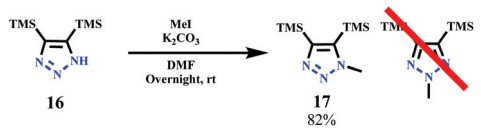


Fig. 3 (Left) DFT-computed relative energies of different tautomers and the energy barrier of the transition state for 4,5-bis(trimethylsilyl)-NH-1,2,3-triazole. (Right) The crystal structure of **16**, showcasing the bond angles of nitrogens.



Scheme 1 Selective *N*-1 methylation of **16**.

bond angle compared to the remaining nitrogen atoms. Correspondingly, we obtained the crystal structure of **16** and were able to assign the position of the N bearing H as 1*H* based on both the bond angles of nitrogens in the triazole ring as well as the hydrogen bonding patterns in the unit cell (Fig. 3-right). Moreover, Wipf *et al.* have reported that the methylation of the *N*-2 tautomer of **16** affords the formation of both *N*-2 and *N*-1 methylate products in a 76 : 24 ratio respectively.[59] However, interestingly in our case the methylation of **16** resulted in the regioselective *N*-1 methylation (**17**) as observed in the crude NMR of the reaction mixture (see the ESI†) without any traces of *N*-2 (Scheme 1). While all other synthesized 1,2,3-triazoles in this work show rapid tautomerization at room temperature, to the best of our knowledge, compound **16** is a rare case that can be obtained exclusively as a 1*H* tautomer through the presented protocol.

Finally, it has been reported that some of the synthesized triazoles in this work show promising biological activities as single molecules. For instance, compound **1** shows stronger indoleamine 2,3-dioxygenase (IDO) inhibitory activity when compared to the most commonly used inhibitor 1-MT,[60] while **6** and **13** respectively show promising metalloenzyme[61] and viral polymerase[62] inhibitory effects. We believe that our work presents a green and more biologically suitable method to synthesize such valuable compounds. Our method is not only catalyst-free, additive-free, and solvent-free, but also provides an atom economical, safer, and more convenient route to synthesize 1,2,3-triazoles. The simple work-up and purification procedure along with its scalability makes this method a potent green route for synthesizing potentially pharmaceutically valuable compounds on a practical scale without any metal contamination.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support by the Loker Hydrocarbon Research Instituted is gratefully acknowledged.

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