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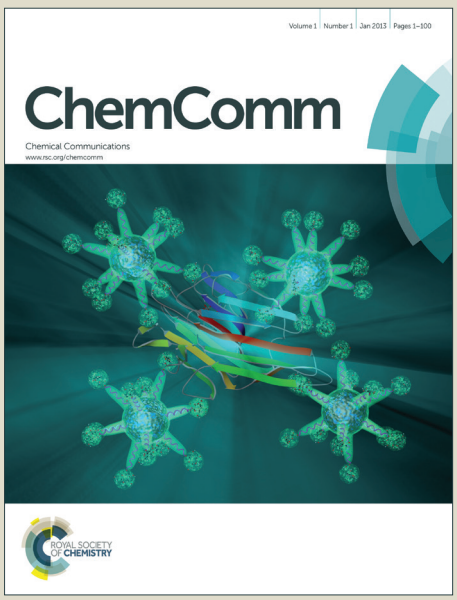

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Efficient One-Pot Strategy for the Highly Regioselective Metal-Free Synthesis of 1,4-Disubstituted-1,2,3-Triazoles†

Akbar Ali,[a] Arlene G. Corrêa,[a] Diego Alves,[b] Julio Zukerman-Schpector,[a] Bernhard Westermann,[c] Marco A. B. Ferreira[a] and Márcio W. Paixão*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A simple and efficient metal-free methodology for the regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles has been developed by applying a novel inverse electron-demand-1,3-dipolar cycloaddition approach. The practical one-pot metal-free strategy can be accomplished with various alkylidene malononitrile and aromatic azides in the presence of base.

The synthesis of chemical entities containing nitrogen heterocycles in a simple and efficient manner has been attracting considerable attention from both segments – of academia and industry.[1] Particularly, 1,2,3-triazoles are a prominent class of heterocycles that exhibit a broad spectra of biological properties, such as antibacterial, anticancer, antivirus and antituberculosis.[2] Besides, the triazole ring has been extensively used as linkage in bioconjugation chemistry due to its easy accessibility, hydrolytic and metabolic stability, water solubility, rigidity and its peptidomimetic character (1,4- and 1,5-disubstituted: *trans* and *cis* peptide mimics respectively).[3] Furthermore, the application of fused and non-fused 1,2,3-triazole frameworks is not limited to the biological field, being also extended to other sectors of the fine chemical industries, e.g. dyes, agrochemicals, corrosion inhibitors and photostabilizers.[4] Due to its manifold applications in the field of life and material sciences, various well-designed methodologies have been already developed to assemble these interesting scaffolds.[5] In particular, the construction of both the 1,4 and 1,5-disubstituted 1,2,3-triazole regioisomers has conventionally been accomplished using 1,3-dipolar cycloaddition of alkynes and organic azides under thermal conditions,[6] mediated by organometallic reagents[7] as well as under copper or ruthenium catalysis[8] – the so-called click chemistry.[9] However, these strategies possess some drawbacks, for example, the thermal Huigsen 1,3-dipolar cycloaddition usually requires high temperatures and provides the formation of both 1,4- and 1,5-triazole regioisomers. Moreover, the use of transition metals as catalysts has restricted their application in chemical biology - because of their eco-adverse effects, e.g. degradation induction of oligonucleotides[10] and polysaccharides.[11] To overcome these limitations, several alternative metal-free strategies, e.g. (a) the base promoted 1,3-cycloaddition reaction of aryl azides with active methylene compounds,[12] (b) the organocatalyzed Ramachary/Bressy/Wang enamide-azide cycloaddtion,[13] (c) the reaction of aryl azides with α-keto phosphorous ylides[14] and (d) the cycloaddition of terminal alkynes with aryl azides in the presence of catalytic amount of tetramethylammonium hydroxide[15] have also been described for the regioselective synthesis of 1,2,3-triazoles. More recently, an elegant modification of the Sakai reaction, through the combination of an amine and α,α-dichlorotosylhydrazones have been reported as a powerful and complementary strategy in metal-free bioorthogonal 1,4-triazole synthesis.[16] Likewise, Cui and co-workers reported a multicomponent cascade reaction for the synthesis of 1,5-disubstituted-1,2,3-triazole via Michael addition/deacylative diazo transfer/cyclization sequence.[17]

Although, numerous methodologies have been designed to construct these moieties by using metal and non-metal approaches (Figure 1) – there is still a huge demand to design a straightforward efficient methodology to obtain selectively the triazole core by metal-free chemistry. Herein we report a novel metal-free strategy to generate selectively 1,4-disubstituted-1,2,3-triazoles by an inverse electron-demand 1,3-dipolar cycloaddition between aryl azides and alkylidenemalonitrile, as well as by one-pot way using aldehyde, malononitrile (equimolar or catalytic amount) and aryl azides under basic conditions.

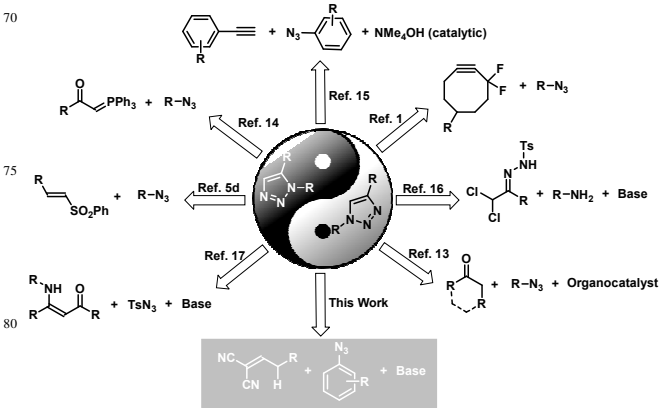
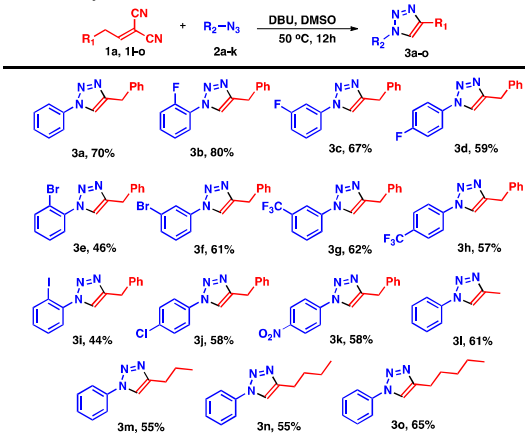


Figure 1: Metal-Free Strategies for the Synthesis of 1,4- and 1,5-Disubstituted-1,2,3-Triazoles.

We initiated our investigation on the model reaction of alkylidene malononitrile **1a** with phenyl azide **2a** under various reaction conditions (See the Supporting Information for full details). These results revealed that both the nature of the base and solvent were critical for this protocol. Therefore, 1,4-disubstituted-1,2,3-triazole **3a** was obtained in 70% isolated yield upon treatment of

1a (0.3 mmol) and phenyl azide **2a** (0.6 mmol) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMSO as solvent at 50 °C for 8 h. With the optimized reaction conditions in hand, we proceeded to examine the scope of this protocol by employing a large variety of alkylidene malononitriles **1k, 1l-o** and aryl azides **2a-k** (Table 1). Alkylidene malononitrile **1a** reacted smoothly with electron-neutral and different electron-deficient aryl azides to give the corresponding 1,4-disubstituted-1,2,3-triazole **3a-k** in good yield. Furthermore, substitution pattern (e.g., *para*-, *meta*-, or *ortho*-) of the electron-withdrawing groups on the aryl azides had little effect on the reactivity (compare: **3b** *vs* **3c** *vs* **3d**). Unfortunately, aryl azides containing electron-donating groups as well as benzyl azide were not compatible with this transformation under the optimal reaction conditions. Additionally, we further evaluated the generality of this metal-free approach exploring the scope of alkylidene malononitriles **1**. Importantly, a series of linear alkylidene malononitriles exhibited comparable reactivity, and good results were generally obtained (Table 1, compounds **3l-o**).

Table 1: Substrate scope of alkylidene malononitriles and aryl azides in the metal-free synthesis of 1,4-disubstituted-1,2,3-triazoles.[a]

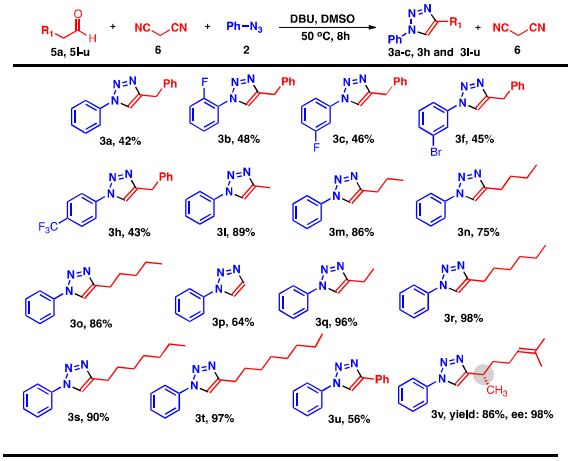


[a]Unless otherwise noted, reactions were performed using alkylidene malononitrile (0.3 mmol), aryl azide (0.6 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 mmol) in 0.5 mL of DMSO. Yields refer to the column-purified products.

In attempts to improve the synthetic scope of our method, the feasibility of carrying out the reaction in a one-pot manner was examined. Appealingly, the one-pot protocol proved to be very effective, and simply mixing the appropriated aldehyde **5a, l-u**, malononitrile **6**, phenyl azide **2a**, with an equimolar amount of DBU, delivered the desired products in high chemical yields (Table 2). This new strategy showed an exelent tolerance to a set of aliphatic aldehydes. Notably, the one-pot protocol enhanced the yield drastically – e.g. when propanal was employed as reaction partner, the yield of the corresponding heterocycle (**3l**) increases from 61% to 89%. Remarkably, this method was also compatible to acetaldehyde, where the monosubstituted triazole ring (**3p**) was furnished in 64% isolated yield. Similarly this prominent efficiency increment is also clear in other examples like **3m-o**. Aldehydes containing even longer linear side chain (**3r-t**) also worked well, leading to a high level of chemical yield. Furthermore, this one-pot strategy also delivered the desired triazol when phenylacetaldehyde was used as reaction partner (**3u**, 56%) Moreover, aryl azides bearing electron-withdrawing substituent were also suitable to this protocol, and the desired products were obtained in good yields. (**3b**, **3c**, **3f** and **3h**).

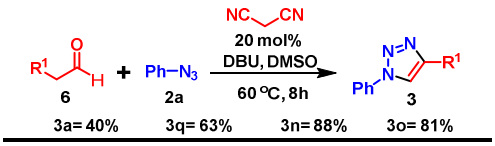
Gratifyingly, the concept can be extended to include the formation of optically active triazoles. The direct and one-pot formation of optically active triazoles thus takes place by reacting the monoterpenoid - (*S*)-(-)-citronellal, malononitrile and phenyl azide in the presence of DBU as base. Despite the presence of base, the desired triazole **3u** system could be obtained in high stereoselectivity and chemical efficiency (yield: 86%, *ee*: 98%).

Table 2: One-pot construction of 1,4-disubstituted-1,2,3-triazoles.[a]



[a]Unless otherwise noted, reactions were performed using aldehyde (0.3 mmol), malononitrile (0.3 mmol), phenyl azide (0.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 mmol) in 0.5 mL of DMSO. Yields refer to the column-purified products. The *ee* was determined by HPLC analysis using chiral stationary phase.

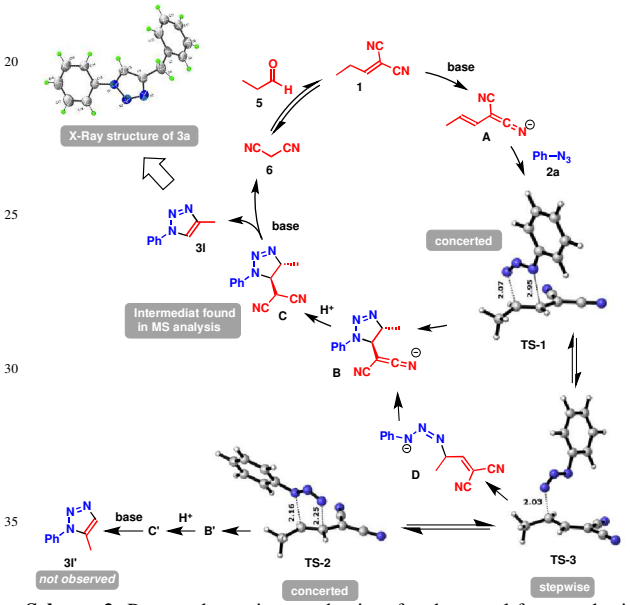
Gratifyingly, it could be demonstred for the catalytic one-pot reaction of **2a** and, a range of aldehydes that only a catalytic amount of malononitrile (20 mol%) is necessary. The reaction took place effectively under the same reaction conditions (Scheme 1). Having malononitrile as organocatalyst, small erosion on the chemical efficiency was observed, however, it appears comprehensive, since no previous optimisation has been done.



Scheme 1: Catalytic strategy for the metal-free synthesis of 1,4-disubstituted-1,2,3-triazoles. Unless otherwise noted, reactions were performed using aldehyde (0.3 mmol), phenyl azide (0.6 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 mmol) and malononitrile (20 mol%) in 0.5 mL of DMSO. Yields refer to the column-purified products.

The product structure, in particular with regard to the regiochemistry was assigned unambiguously by 2D NMR spectroscopy and X-ray crystallography (See the Supporting Information). Based on the above achievements as well as with DFT calculations, and MS-analysis, a proposed reaction mechanism for this transformation is depicted in Scheme 2. We have computed both concerted and stepwise mechanism for the PhN_3 (**2a**) and vinylogous carbanion (**A**). Regarding the one-pot approach, the sequence is triggered by a Knoevenagel condensation of malononitrile (**6**) and aliphatic aldehydes (**5**) that generates the alkylidene malononitriles (**1**). Next, in the presence

of a strong base (DBU), compound (**1**) can be deprotonate to furnish vinylogous carbanion **A**. Subsequently intermediated **A** operates as the electron-rich olefinic partner that reacts with aryl azide **2a**. Among the concerted transition states, **TS-1** was the lowest in energy (presenting high asynchronicity, and an energy barrier of 23.5 kcal mol^{-1}), which furnishes the protonated cycloaddition adduct **C** (detected by MS analysis). **TS-2**, that leads to the unobserved regioisomer **3l'**, is disfavoured by 11.6 kcal mol^{-1}. Moreover, **TS-3** (related to the first step of the stepwise mechanism leading to the observed regioisomer **3l**) is disfavoured by 2.4 kcal.mol^{-1} in energy, resulting in a zwitterionic intermediate **D**. We were not able in characterize the ring closure to the intermediate **B**. Finally; a *syn*-elimination step from **C** delivers the final product (**3l**) and recycles malononitrile (**6**). The aromatization of the triazole ring is the potential driving force of the reaction. A full energy profile can be seen in SI – Figure S2..



Scheme 2: Proposed reaction mechanism for the metal-free synthesis of 1,4-disubstituted-1,2,3-triazoles.[18]

The observed regioselectivity was analysed applying the general distortion/interaction theory proposed by Houk and Ess.[19] The distortion/interaction model divides the activation energy ($\Delta E^{\ddagger}$) of a 1,3-dipolar reaction in two parts: the energy required to distort the fragments (dipole and dipolarophile) ($\Delta E_d^{\ddagger}$), and the interaction energy ($\Delta E_i^{\ddagger}$) between them.

The activation energy is $\Delta E^{\ddagger} = \Delta E_d^{\ddagger} + \Delta E_i^{\ddagger}$. We observe that the $\Delta\Delta E_d^{\ddagger}$ (total) between **TS-1** and **TS-2** is very small (1.1 kcal mol^{-1}) (See Table S-1 on SI for further details). We can conclude that the exclusive formation of **3l** arises from the more favorable HOMO-LUMO interaction, driven by the match between the largest orbital coefficients (see (Figure S-5 on SI), in which the $\Delta\Delta E_i^{\ddagger}$ is 10.6 kcal mol^{-1}. In summary we present a significant addition to the regioselective construction of 1,4-substiuted-1,2,3-triazoles by the assistance of active alkylidenes. This method has proven successful by using preformed alkylidene malononitriles and a range of aryl azides. Therefore, natural products exhibiting an acetaldehyde moiety should be amenable for this modification without further manipulation. This route is operationally straightforward, and simple to carry out in its one-pot version. The inherently benign nature and efficient assembly of the triazole moiety render this protocol ideal and expected to lead to interesting application. The authors gratefully acknowledge FAPESP (09/07281-0, 09/54040-8, and 13/02311-3) and CNPq (INCT-Catálise, INBEQMeDI, and 477944/2013-2) for financial support. Calculations were performed at CENAPAD-SP. A.A acknowledges CNPQ-TWAS for the fellowship and Prof. Dr. Timothy J. Brocksom for the suggestion on the manuscript.

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[a] *Department of Chemistry, Universidade Federal de São Carlos (UFSCar), São Carlos, SP, Brazil Fax: 551633518075; Tel: 551633518075; E-mail: mwpaixao@ufscar.br*

[b] *Department of Chemistry, Universidade Federal de Pelotas (UFPel), Pelotas, RS, Brazil.*

[c] *Department of Bioorganic Chemistry, Leibniz-Institute of Plant and Biochemistry, Halle, Germany.*

† Electronic Supplementary Information (ESI) available: Reaction conditions, spectras, absolute energies, and cartesian coordinates of calculated structures. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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