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SHORT COMMUNICATION

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A Facile One-Pot Metal-Free Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

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A 1,3-dipolar cycloaddition reaction of commercially available aldehydes with azides and secondary amines through a one-pot strategy has been developed. This method furnishes 1,4-disubstituted 1,2,3-triazoles in good to excellent yields and high levels of regioselectivity.

Introduction

1,2,3-Triazoles were considered as useful synthons to transform into various medicinally important molecules.[1] Figure 1 shows TSAO ("*tert*-butyldimethylsilylspiroaminooxathioledioxide"), a non-nucloside reverse-transcriptase inhibitor,[2] and CAI ("carboxyamidotriazole"), which exhibits anticancer activity.[3] 1,2,3-Tiazole moieties are also known as HIV protease inbibitors[4] and demonstrate potential antituberculosis bioactivity.[5] Therefore, the development of rapid and efficient protocols for the construction of diversified triazoles tends to be extremely demanded.

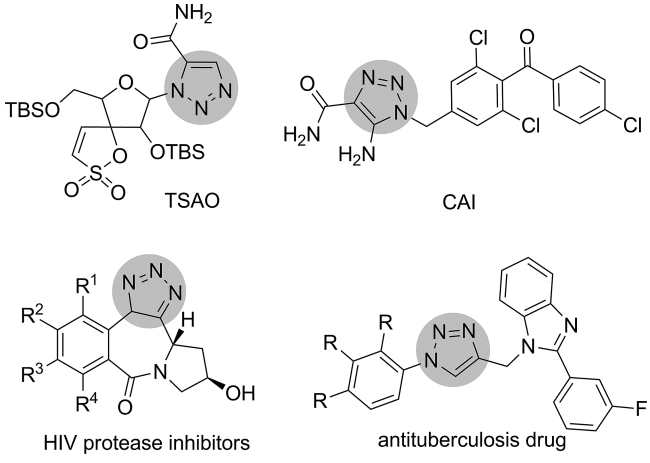
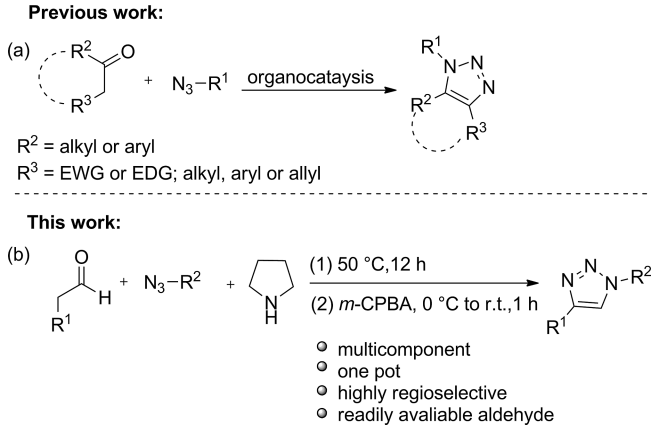


Figure 1. Selected biologically important 1,2,3-triazoles.

Even though the thermally induced 1,3-dipolar cycloaddition of alkynes with azides has been known for over one century to make 1,2,3-triazoles and further developed by Huisgen,[7] these compounds came into the limelight only in the last two decades due to their excellent copper-catalyzed regioselective synthesis developed by the Sharpless[6] and Meldal[8a] groups. Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction provides an advantage of straightforward and powerful approaches to prepare 1,4-disubstituted 1,2,3-triazoles with high yields and regioselectivities.[8] However, Cu^{I} can cause oxidative DNA degradation[9] and is potentially toxic for living organisms.[10] Therefore, the development of precise syntheses of 1,2,3-triazoles without use of metals is a significant responsibility for organic chemists.

In recent years, Ramachary,[11] Bressy,[12] our group[13] and other groups[14] independently reported the use of small organic molecules as catalysts to react with organic azides and carbonyl compounds to afford substituted 1,2,3-triazoles with high levels of regioselectivities (Scheme 1a).[14] As part of our continued interest in extending substrate scope and diversity of 1,2,3-triazoles, we present our new results of azides with commercially available aldehydes and



Scheme 1. Organocatalytic strategies in the preparation of 1,2,3-triazoles.

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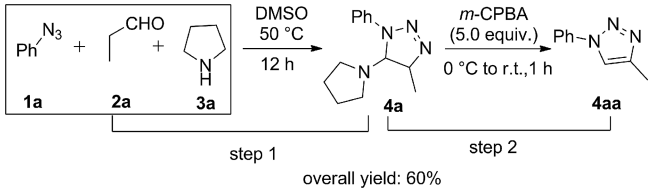
secondary amines (via the enamine intermediate formed in situ) to construct 1,4-disubstituted 1,2,3-triazole compounds[15] (Scheme 1b), even though the Ramachary group had recently reported an elegant progress in the organocatalytic enolate-mediated synthesis of 1,2,3-triazoles from aldehydes or ketones with aryl azides.[11c,11d]

Results and Discussion

We began our initial investigation by a two-step synthesis employing phenyl azide (**1a**), propionaldehyde (**2a**) and pyrrolidine (**3a**) in DMSO. After 12 h, 4-methyl-1-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (**4a**) was successfully obtained after flash chromatography; then **4a** was submitted to Cope elimination in the presence of *m*-chloroperoxybenzoic acid (*m*-CPBA) to afford the desired 1,4-disubstituted 1,2,3-triazole **4aa**. The two-step synthesis provided **4aa** in an overall 60% yield. To further improve the efficiency, we propose a one-pot strategy merging step 1 and step 2 to form **4aa** in high yield without isolating intermediate **4a** (Scheme 2).



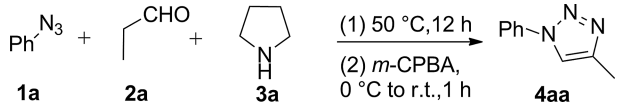
Scheme 2. Synthesis of 1,4-disubstitued 1,2,3-triazoles in one pot.

To test the feasibility of this hypothesis, the reaction between phenyl azide (**1a**), propionaldehyde (**2a**) and pyrrolidine (**3a**) was chosen as the model to optimize the reaction parameters. As shown in Table 1, the reaction was carried out in various solvents (Table 1, Entries 1–6). To our delight, excellent yields were achieved in THF (Entry 4, 12 h, 98%). Then we examined the effect of the substrate ratio of **1a**/**2a**/**3a**. The results indicated that a ratio of **1a**/**2a**/**3a** = 1.0:1.1:1.0 resulted in both, a quantitative yield and a short reaction time (Table 1, Entry 8). Lowering of the concentration of starting material **1a** to 1.0 mol/L showed no significant drop in yield (Table 1, Entry 10). Although conducted at room temperature, a 78% yield was still achieved in 12 h (Table 1, Entry 11). It is also worth noting that the desired product **4aa** was obtained as a single regioisomer. The configuration was assigned unambiguously by X-ray analysis of the product **4aa**.[16]

Then we turned our attention to investigate the effect of secondary amines in the reaction (Table 2). Other five- and six-membered cyclic and acyclic secondary amines were screened, and it was found that five-membered cyclic amines (especially pyrrolidine **3a**) gave the best yield (99%; Table 2, Entry 1). Reactions in the presence of **3b**, **3c** and **3f** as the catalysts did not afford the desired product.

With the optimized reaction conditions in hand, we then examined the scope of azides **1** and acetaldehydes **2** in the presence of pyrrolidine **3a**. As summarized in Table 3, phenyl azide (**1a**), acetaldehydes **2** and pyrrolidine (**3a**) were allowed to react in one pot under optimal conditions to give the desired 1,4-disubstitued 1,2,3-triazols in moderate to high yields. Acetaldehydes bearing aliphatic and aro-

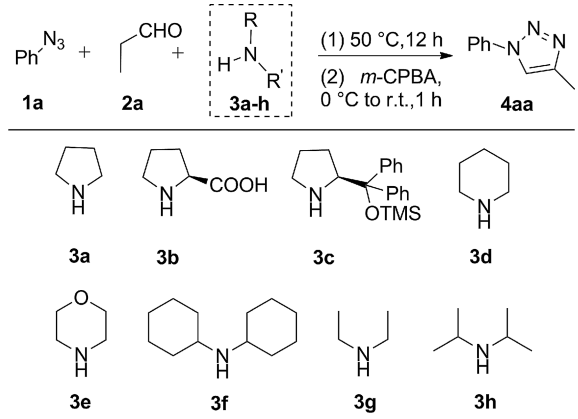
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	*T* [°C]	Ratio of **1a**/**2a**/**3a**	*t* [h]	Yield [%][b]
1	CH_3CN	50	1.0:2.0:1.0	60	77
2	$CHCl_3$	50	1.0:2.0:1.0	60	85
3	MeOH	50	1.0:2.0:1.0	60	76
4	THF	50	1.0:2.0:1.0	12	98
5	toluene	50	1.0:2.0:1.0	60	95
6	DCE	50	1.0:2.0:1.0	60	90
7	THF	50	2.0:1.0:1.0	12	98
8	THF	50	1.0:1.1:1.0	12	99
9	THF	50	1.0:1.1:2.0	12	98
10[c]	THF	50	1.0:1.1:1.0	12	93
11	THF	r.t.	1.0:2.0:1.0	12	78

[a] Reaction conditions: A mixture of **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), **3a** (0.2 mmol, 1.0 equiv.) in solvent (0.5 mL) was stirred at 50 °C for 12 h. After the reaction was complete as monitored by TLC, *m*-CPBA (1.5 equiv.) was added at 0 °C and the mixture warmed up to room temperature for 1 h. [b] Yield of isolated product after column chromatography. [c] Concentration of **1a**: 0.1 M.

Table 2. Effect of the secondary amine.[a]

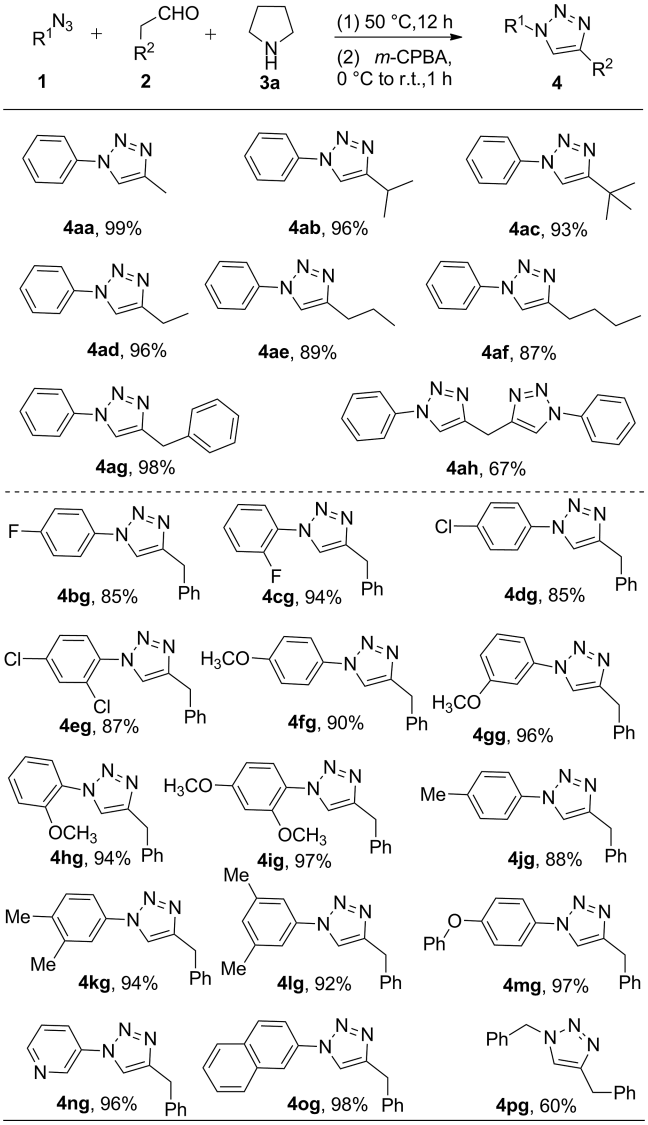


Entry	Amine	Yield [%][b]
1	**3a**	99
2	**3b**	–[c]
3	**3c**	–[c]
4	**3d**	60
5	**3e**	55
6	**3f**	–[c]
7	**3g**	72
8	**3h**	16

[a] Reaction conditions: A mixture of **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), **3a**–**h** (0.2 mmol, 1.0 equiv.) in THF (0.5 mL) was stirred at 50 °C for 12 h. After the reaction was complete as monitored by TLC, *m*-CPBA (1.5 equiv.) was added at 0 °C and the mixture warmed up to room temperature for 1 h. [b] Yield of isolated product after column chromatography. [c] No reaction.

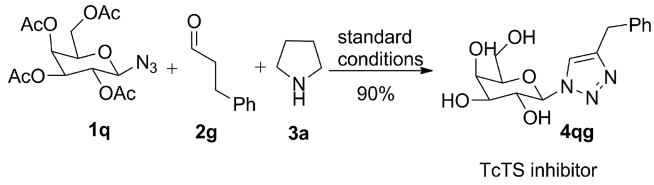
matic groups also reacted smoothly to afford the desired products in satisfying yields (Table 3, **4aa**–**4ah**, 67–99%). To our delight, various substituted azides, regardless of the substitution patterns (with electron-withdrawing or -donating groups), afforded the corresponding products in good to excellent yields (Table 3, **4bg**–**4 mg**, 85–97%). It is noteworthy that heterocycles such as pyridine and naphthalenes were also tolerated as substrates to afford the desired products in high yields (Table 3, **4ng** and **4og**, 96% and 98%, respectively). In addition, the less reactive benzyl azide (**1p**) produced 1,4-dibenzyl-1,2,3-triazole in moderate yield (Table 3, **4pg**, 60%).

Table 3. Scope of substrate.[a]



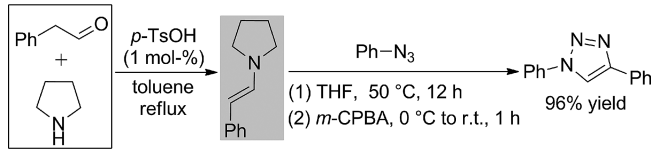
[a] Reaction conditions: A mixture of **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.4 mmol, 2.0 equiv.), **3a** (0.2 mmol, 1.0 equiv.) in THF (0.5 mL) was stirred at 50 °C for 12 h. After the reaction was complete, *m*-CPBA (1.5 equiv.) was added at 0 °C and the mixture warmed up to room temperature for 1 h.

To further investigate the generality and potential of our protocol, we undertook the formal synthesis of Trypanosoma cruzi *trans*-sialidase (TcTS) inhibitor.[17] A mixture of azide **1q**, 3-phenylpropanal (**2g**) and pyrrolidine (**3a**) was allowed to react under the standard conditions to lead to an intermediate, which was easily converted in the presence of sodium methoxide into the target TcTS inhibitor **4qg** (Scheme 3, 90% yield). Consequently, the presented method provides a convenient and high-yielding process for the synthesis of 1,4-disubstituted triazole derivatives.

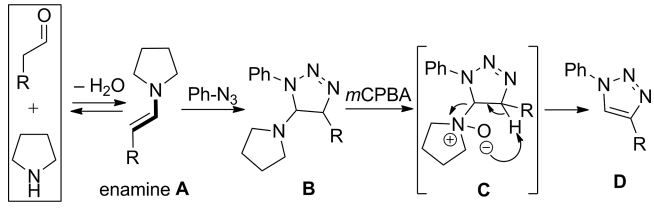


Scheme 3. Synthesis of Trypanosoma cruzi *trans*-sialidase (TcTS) inhibitor.

To approve the proposed structure of the enamine intermediate, a reaction of phenylacetaldehyde (**2i**) and pyrrolidine (**3a**) was conducted in the presence of TsOH and succeeded to form the enamine intermediate,[18] which was followed by reaction with phenyl azide (**1a**) to afford the desired product in 96% yield (Scheme 4). Build upon these data, a mechanism is proposed and depicted in Scheme 5. Condensation of acetaldehyde and pyrrolidine generates enamine **A**, which then reacts with phenyl azide (**1a**) through a Huisgen 1,3-dipolar cycloaddition to afford the key intermediate **B**. A subsequent oxidation of **B** leads to *N*-oxide **C**. Finally, intermediate **C** is converted into the expected triazole **D** by an elimination process.[13a]



Scheme 4. Reaction of the in situ formed enamine with azide.



Scheme 5. Plausible mechanism.

Conclusions

We have developed a new method to efficiently prepare 1,4-disubstituted 1,2,3-triazoles from organic azides, commercially available aldehydes and cheap secondary amines by a one-pot strategy in good to high yields and excellent levels of regioselectivities. To demonstrate the utility of this chemistry, several biologically important molecules were synthesized. Considering the ready availability of the starting materials and the operational simplicity, we believe that this method will have a broad application both in academy

and industry. Further mechanistic studies and applications of this methodology are in progress, and more results will be reported in due course.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Mercury-Plus 300 (300 MHz) or a Bruker ACF400 spectrometer (400 MHz and 101 MHz). Chemical shifts for protons are reported in ppm downfield from the tetramethylsilane signal and are referenced to residual ^{1}H in the NMR solvent ($CHCl_3$: δ = 7.26 ppm). Chemical shifts for carbons are reported in ppm downfield from the tetramethylsilane signal and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ = 77.16 ppm). Data are represented as follows: chemical shift, multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), integration. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with UV light of 254 nm. Further visualization was achieved by staining with iodine. Flash chromatography separations were performed on Merck 60 mesh (0.040–0.063 mm) silica gel.

Typical Procedure for the Synthesis of 4aa: To a solution of THF (0.5 mL) were added amine **3a** (0.20 mmol), aldehyde **2a** (0.22 mmol), and azide **1a** (0.20 mmol). The reaction mixture was stirred at 50 °C for 12 h. After the reaction was complete, 1.5 equiv. of *m*-CPBA was added to the reaction mixture at 0 °C and the mixture warmed up to room temperature for 1 h. The reaction mixture was then concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel (hexane/EtOAc, 10:1 to 5:1) to afford the desired product **4aa**.

4aa: White solid (yield 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.47 (t, J = 15.6 Hz, 2 H), 7.38 (t, J = 14.8 Hz, 1 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.00, 137.13, 129.63, 128.38, 120.24, 119.46, 77.55, 77.23, 76.91, 10.78 ppm.

4ab: White solid (yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.68 (m, 3 H), 7.48 (t, J = 7.2 Hz, 2 H), 7.42–7.32 (m, 1 H), 3.23–3.10 (m, 1 H), 1.37 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.22, 137.29, 129.60, 128.32, 120.33, 117.54, 77.49, 77.17, 76.85, 29.67, 25.87, 22.48 ppm.

4ac: White solid (yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.68 (m, 3 H), 7.54–7.45 (m, 2 H), 7.44–7.36 (m, 1 H), 2.83 (q, J = 22.8 Hz, 2 H), 1.34 (t, J = 15.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.52, 137.28, 129.64, 128.39, 120.37, 118.48, 77.42, 77.10, 76.78, 19.05, 13.63 ppm.

4ad: Light yellow oil (yield 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.67 (m, 3 H), 7.53–7.45 (m, 2 H), 7.44–7.36 (m, 1 H), 2.77 (t, J = 15.2 Hz, 2 H), 1.71–1.76 (m, 2 H), 1.01 (t, J = 14.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.92, 137.27, 129.63, 128.37, 120.33, 118.88, 77.43, 77.11, 76.79, 27.65, 22.64, 13.78 ppm.

4ae: Light yellow oil (yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.67 (m, 3 H), 7.49 (t, J = 15.6 Hz, 2 H), 7.40 (d, J = 7.6 Hz, 1 H), 2.85–2.72 (m, 2 H), 1.72 (dt, J = 15.3, 7.6 Hz, 2 H), 1.43 (dq, J = 14.6, 7.4 Hz, 2 H), 0.95 (t, J = 14.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.15, 137.30, 129.64, 128.37, 120.36, 118.79, 77.39, 77.07, 76.76, 31.50, 25.35, 22.31, 13.81 ppm.

4af: Light yellow solid (yield 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 2 H), 7.60 (s, 1 H), 7.44 (t, J = 15.2 Hz, 2 H), 7.37 (d, J = 7.3 Hz, 1 H), 7.33–7.18 (m, 5 H), 4.15 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.43, 138.86, 137.16, 129.67, 128.80, 128.73, 128.53, 126.65, 120.38, 119.72, 77.48, 77.16, 76.85, 32.29 ppm.

4ag: White solid (yield 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 2 H), 7.73 (d, J = 8.0 Hz, 4 H), 7.51 (t, J = 15.2 Hz, 4 H), 7.43 (t, J = 14.8 Hz, 2 H), 4.38 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.80, 137.10, 129.74, 128.70, 120.49, 120.20, 77.35, 77.24, 77.04, 76.72, 22.91 ppm.

4ah: White solid (yield 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.71 (s, 2 H), 7.52–7.49 (m, 2 H), 7.43–7.35 (m, 1 H), 1.42 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.34, 137.36, 129.60, 128.31, 120.41, 116.81, 77.41, 77.09, 76.77, 30.85, 30.32 ppm.

4bg: White solid (yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 2 H), 7.57 (s, 1 H), 7.34–7.28 (m, 4 H), 7.26–7.19 (m, 1 H), 7.18–7.09 (m, 2 H), 4.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.49, 161.02, 148.58, 138.76, 133.47, 133.44, 128.78, 128.75, 126.68, 122.37, 122.29, 119.89, 116.70, 116.47, 77.48, 77.16, 76.84, 32.25 ppm.

4cg: Light yellow solid (yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (td, J = 7.8, 1.7 Hz, 1 H), 7.72 (d, J = 2.9 Hz, 1 H), 7.40–7.33 (m, 1 H), 7.33–7.18 (m, 7 H), 4.17 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.53, 152.04, 147.99, 138.77, 130.03, 129.95, 128.76, 128.71, 126.63, 125.21, 125.17, 124.82, 122.81, 122.73, 117.05, 116.85, 77.49, 77.17, 76.85, 32.19 ppm.

4dg: White solid (yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dt, J = 4.0, 2.4 Hz, 3 H), 7.46–7.38 (m, 2 H), 7.35–7.27 (m, 4 H), 7.26–7.17 (m, 1 H), 4.14 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.73, 138.68, 135.63, 134.21, 129.82, 128.78, 128.77, 126.72, 121.50, 119.59, 77.47, 77.15, 76.83, 32.26 ppm.

4eg: Light yellow solid (yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (s, 1 H), 7.52 (dd, J = 8.2, 5.4 Hz, 2 H), 7.37 (dd, J = 8.8, 2.4 Hz, 1 H), 7.34–7.27 (m, 4 H), 7.26–7.19 (m, 1 H), 4.17 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.64, 138.66, 135.99, 133.73, 130.51, 129.29, 128.75, 128.73, 128.48, 128.23, 126.68, 123.51, 77.49, 77.17, 76.85, 32.16 ppm.

4fg: White solid (yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.49 (m, 3 H), 7.31 (d, J = 4.4 Hz, 4 H), 7.27–7.16 (m, 1 H), 7.01–6.89 (m, 2 H), 4.14 (s, 1 H), 3.81 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.66, 148.19, 138.96, 130.66, 128.79, 128.70, 126.60, 122.02, 119.87, 114.69, 77.45, 77.13, 76.82, 55.60, 32.31 ppm.

4gg: Light yellow solid (yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H), 7.36–7.27 (m, 6 H), 7.26–7.19 (m, 1 H), 7.19–7.14 (m, 1 H), 6.90 (dd, J = 8.4, 2.4 Hz, 1 H), 4.14 (s, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.56, 148.36, 138.85, 138.17, 130.43, 128.79, 128.73, 126.64, 119.79, 114.37, 112.25, 106.20, 77.49, 77.18, 76.86, 55.60, 32.27 ppm.

4hg: Light yellow solid (yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.72 (dd, J = 7.9, 1.6 Hz, 1 H), 7.39–7.26 (m, 5 H), 7.26–7.16 (m, 1 H), 7.09–6.95 (m, 2 H), 4.17 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.15, 146.80, 139.20, 129.95, 128.78, 128.61, 126.47, 125.47, 123.74, 121.15, 112.26, 77.49, 77.17, 76.86, 55.95, 32.25 ppm.

4ig: Light yellow solid (yield 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.37 (d, J = 3.2 Hz, 1 H), 7.34–7.27 (m, 4 H), 7.26–7.17 (m, 1 H), 6.92 (dt, J = 9.1, 6.0 Hz, 2 H), 4.16 (s, 2 H), 3.77 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.86, 146.88, 144.90, 139.17, 128.76, 128.61, 126.47, 123.71, 115.43, 113.67, 110.36, 77.51, 77.19, 76.87, 56.53, 55.93, 32.23 ppm.

4jg: Light yellow solid (yield 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 4.4 Hz, 4 H), 7.26–7.18 (m, 3 H), 4.14 (s, 2 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.25, 138.94, 138.57, 134.90, 130.15, 128.80, 128.71, 126.61, 120.28, 119.69, 77.49, 77.17, 76.85, 32.31, 21.06 ppm.

4kg: Light yellow solid (yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 7.45 (d, J = 1.9 Hz, 1 H), 7.36–7.27 (m, 5 H), 7.26–7.20 (m, 1 H), 7.17 (d, J = 8.1 Hz, 1 H), 4.14 (s, 2 H), 2.27 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.17, 138.98, 138.22, 137.23, 135.10, 130.54, 128.81, 128.70, 126.59, 121.53, 119.72, 117.67, 77.49, 77.17, 76.86, 32.32, 19.86, 19.43 ppm.

4lg: Light yellow solid (yield 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 7.34–7.26 (m, 6 H), 7.26–7.19 (m, 1 H), 7.00 (s, 1 H), 4.15 (s, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.22, 139.57, 138.94, 137.06, 130.13, 128.81, 128.71, 126.60, 119.78, 118.19, 77.47, 77.15, 76.83, 32.33, 21.28 ppm.

4mg: White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 3 H), 7.28 (m, 1 H), 7.26–7.16 (m, 6 H), 7.10 (s, 1 H), 5.44 (s, 2 H), 4.05 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.08, 139.06, 134.86, 129.06, 128.71, 128.61, 127.96, 126.48, 121.36, 77.41, 77.10, 76.78, 54.05, 32.32, 29.72 ppm.

4ng: White solid (yield 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.51 (m, 3 H), 7.38–7.26 (m, 6 H), 7.26–7.19 (m, 1 H), 7.13 (t, J = 7.4 Hz, 1 H), 7.08–6.98 (m, 4 H), 4.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.63, 156.44, 148.41, 138.89, 132.44, 130.04, 128.82, 128.75, 126.67, 124.10, 122.13, 119.89, 119.35, 119.31, 77.51, 77.19, 76.87, 32.31 ppm.

4og: White solid (yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 8.64 (d, J = 3.5 Hz, 1 H), 8.20–7.97 (m, 1 H), 7.71 (s, 1 H), 7.44 (dd, J = 8.2, 4.7 Hz, 1 H), 7.38–7.28 (m, 4 H), 7.27–7.20 (m, 1 H), 4.17 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.67, 149.00, 141.41, 138.51, 128.77, 128.75, 127.85, 126.75, 124.20, 119.65, 77.51, 77.19, 76.87, 32.20 ppm.

4pg: Brown solid (yield 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.91 (m, 1 H), 7.88 (d, J = 7.6 Hz, 1 H), 7.59 (d, J = 8.3 Hz, 1 H), 7.54–7.44 (m, 5 H), 7.33 (dt, J = 15.1, 7.4 Hz, 4 H), 7.22 (dd, J = 8.1, 6.1 Hz, 1 H), 4.23 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.67, 138.95, 134.15, 133.88, 130.24, 128.85, 128.77, 128.56, 128.27, 127.82, 127.02, 126.67, 124.97, 124.25, 123.47, 122.44, 77.51, 77.19, 76.87, 32.34 ppm.

Procedure for Synthesis of Trypanosoma cruzi *trans*-Sialidase (TcTS) Inhibitor: To THF (0.5 mL) were added pyrrolidine **3a** (0.20 mmol), 3-phenylpropanal (**2g**) (0.22 mmol) and (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-azidotetrahydro-2*H*-pyran-3,4,5-triyltriacetate (**1q**) (0.20 mmol). The reaction mixture was stirred at 50 °C for 12 h. After the reaction was complete, *m*-CPBA (1.5 equiv.) was added at 0 °C and the mixture warmed up to room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (hexane/EtOAc, 10:1 to 5:1) to afford the desired product **4qg**.

4qg: White solid (yield 94%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.91 (s, 1 H), 7.33–7.25 (m, 4 H), 7.25–7.18 (m, 1 H), 5.57 (d, J = 9.2 Hz, 1 H), 4.08 (s, 2 H), 3.93–3.84 (m, 2 H), 3.71 (dd, J = 12.2, 5.2 Hz, 1 H), 3.61–3.53 (m, 2 H), 3.53–3.44 (m, 1 H), 3.33 (dd, J = 3.1, 1.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 147.10, 138.87, 128.31, 128.26, 126.16, 121.67, 88.14, 79.68, 77.10, 72.54, 69.46, 60.96, 47.85, 47.64, 47.42, 31.21 ppm.

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

Acknowledgments

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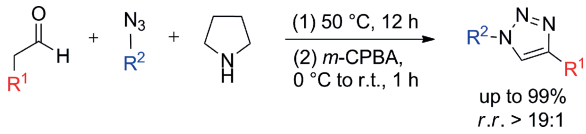
Triazole Synthesis



A one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles by 1,3-dipolar cycloaddition reaction has been developed. This strategy provides a rapid and efficiency way to construct 1,4-disubstitued 1,2,3-triazoldes in good to excellent yields and high levels of regioselectivity (r.r. = ratio of regioisomers).

Keywords: Metal-free synthesis / Triazoles / Azides / 1,3-Dipolar cycloaddition

