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A Scalable, Metal-, Azide- and Halogen-Free Method for the Preparation of Triazoles

Peter R. Clark,*[a][b] Glynn D. Williams,[a] Jerome F. Hayes,[a] and Nicholas C. O. Tomkinson[b]

Abstract: *A scalable, metal-, azide- and halogen-free method for the synthesis of substituted 1,2,3-triazoles has been developed. The reaction proceeds through a 3-component coupling of α-ketoacetals, tosyl hydrazide, and a primary amine. Functional group tolerance is outstanding in both the α-ketoacetal and amine coupling partners providing access to 4-, 1,4-, 1,5-, and 1,4,5-substituted triazoles in excellent yield. This robust method results in densely functionalised 1,2,3-triazoles that remain challenging to prepare by azide-alkyne cycloaddition (AAC, CuAAC, RuAAC) methods and can be scaled in either batch or flow reactors. Methods for the chemoselective reaction of either aliphatic amines or anilines are also described revealing some of the potential of this novel and highly versatile transformation.*

The 1,2,3-triazole motif is an important heterocycle with applications in chemical biology, materials chemistry, agrochemicals and pharmaceuticals.[1] This scaffold is highly prevalent in experimental drug candidates and several marketed drug molecules which are used to treat varied clinical indications.[2] Examples include the monosubstituted antibiotics Tazobactam **1** and Cefatrizine **2**, the disubstituted anticonvulsant Rufinamide **3** and the trisubstituted oncology candidate JNJ-54175446 **4** which is currently in clinical trials[3] (Figure 1a). The diversity in substitution of **1**–**4** shows there is a strong demand for robust methods to access all possible substitution patterns of this heterocyclic core.

The most common method to access 1,2,3-triazoles is the Huisgen [3+2] cycloaddition between azide **5** and an alkyne **6** coupling partners.[4] It has been shown that this cycloaddition process can be accelerated with transition metal catalysts.[5] Of great relevance in this area are the CuAAC and RuAAC click reactions, pioneered by Sharpless and Meldal, which deliver the 1,4- and 1,5-regioisomeric products respectively (Figure 1b).[5–6] These transformations have revolutionised chemical biology by providing a robust, efficient and versatile tool that has been applied to solve many challenges within the field.[7] Whilst the cycloaddition approach is undoubtedly important to prepare this class of heterocycle, the requirement for a transition metal catalyst prevents the use of AAC technology in live cells. To address this shortfall, strain promoted azide-alkyne cycloaddition (SPAAC) has been developed providing an invaluable method to conjugate biologically relevant targets.[8] Both cycloaddition strategies require the use of an azide coupling partner. Replacement of the azide with a primary amine nucleophile, the most common commercially available nitrogen containing substrate, is of great interest to the synthetic community.[9]

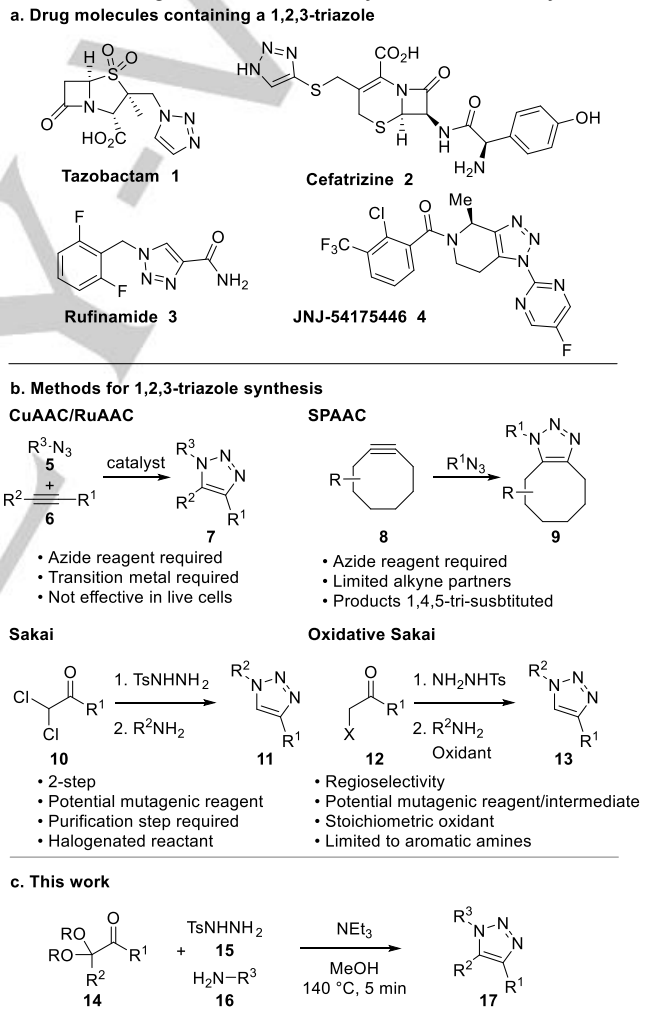

Figure 1. a) Marketed and experimental drugs containing the 1,2,3-triazole motif. b) Methods to synthesise 1,2,3-triazoles. c) One-pot method for the preparation of 1,2,3-triazoles.

In 1986 Sakai reported the synthesis of substituted 1,2,3-triazoles **11** through the reaction of an *α,α*-dichloroketone **10**, tosylhydrazide and a primary amine (Figure 1b).[10] The scope of this transformation was explored by Westermann[11] and demonstrated on scale by Hanselmann,[12] providing a novel process to form this heterocyclic core. However, several

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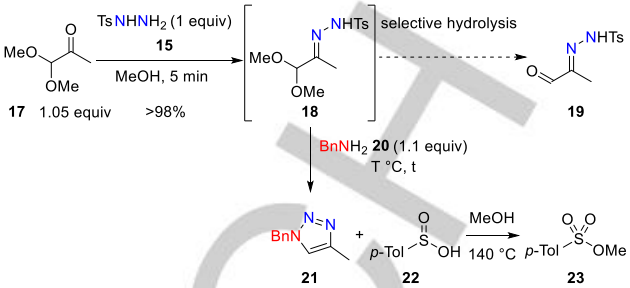
limitations exist with this methodology. These include the requirement to isolate and purify the *α,α*-dichlorohydrazone intermediate resulting in a two-step synthesis of the triazole and the necessity to use a potentially mutagenic halogenated reagent/intermediate. Due to these challenges, this methodology has seen a limited uptake to date. To address some of these problems oxidative variants have been developed (**12**→**13**),[13] however, they suffer from additional drawbacks providing an opportunity for further development.

We believed that under appropriate reaction conditions the α-ketoacetal functionality **14** could act as an effective surrogate for the problematic α,α-dichloroketone providing a significantly more versatile method to prepare substituted 1,2,3-triazole products (Figure 1c). Within this manuscript we show that α-ketoacetals **14** can be reacted with *N*-tosylhydrazide **15** and a primary amine **16** in a 3-component coupling procedure to provide access to mono-, di- and tri-substituted 1,2,3-triazoles in a robust and efficient procedure. The reaction proved to be amenable to scale-up and the protocol was successfully transferred to a flow reactor.

Reaction of α-ketoacetal **17** (1.05 equiv) with tosylhydrazide **15** (1 equiv) in methanol for 5 minutes at room temperature gave the hydrazone **18** (>98%). Selective hydrolysis of the acetal moiety of **18** in the presence of the hydrazone group proved challenging and we were unable to isolate an analytically pure sample of the aldehyde **19**. However, we were delighted to discover that treatment of the crude methanolic solution containing **18** with benzylamine **20** (1.1 equiv) at room temperature and stirring the reaction mixture for a further 16 h gave the triazole **21** in 47% yield (Table 1, Entry 1). Heating the reaction mixture at reflux for 16 h increased the observed yield of **21** to 75% (Entry 2). Increasing the temperature to 120 °C in a sealed reaction vessel gave the product in 83% after 20 minutes (Entry 3) and shortening the time to just 5 minutes gave the product in similar yield (Entry 5, 82%). Increasing the number of equivalents of benzylamine (2.0 equiv) had no significant effect on the reaction outcome (Entry 4, 84%), however, raising the temperature to 140 °C gave the triazole product in 89% after 5 minutes (Entry 6). Under the reaction conditions (MeOH, 140 °C) the sulfinic acid co-product **22** was converted to methyl 4-methylbenzenesulfonate **23** which had to be separated from the triazole product **21** by column chromatography.[14] Conducting the reaction in the presence of triethylamine (1.1 equiv) shut down this pathway and allowed for removal of the sulfinate salt through aqueous workup, simplifying the purification of the product **21** (*cf*. Entry 6 *vs* 7). This simple and effective protocol allowed access to the triazole **21** through reaction of α-ketoacetal **17**, *N*-tosylhydrazide **15** and benzylamine **20** in a 1-pot procedure. This method provides a novel metal-, azide- and halogen-free process for the preparation of this important class of heterocyclic product.

Table 1. Optimisation of triazole synthesis using ketoacetal, tosylhydrazide and benzylamine.



Entry	Temperature T	Time t	Variations	**21** yield[a]
1	rt	16 h	-	47%
2	Reflux	16 h	-	75%
3	120 °C	20 min	-	83%
4	120 °C	20 min	$BnNH_2$ (2.0 equiv)	84%
5	120 °C	5 min	-	82%
6	140 °C	5 min	-	89%
7	140 °C	5 min	Et_3N (1.1 equiv)	88% (88% isolated)

[a]solution yield calculated using internal standard by ^{1}H NMR spectroscopy.

A series of aliphatic amines were examined under the optimised reaction conditions (Scheme 1). Linear aliphatic amines (*n*-propyl- **24**, methyl- **25**), branched sterically encumbered amines (*iso*propyl-, cyclopropyl, cyclohexyl and *tert*butyl, **26**–**29**) and a fluorinated analogue (**30**) all proved suitable substrates to deliver the *N*-alkyl triazole in excellent yields (79–98%). Products that are challenging to prepare using an AAC strategy were also readily accessible using our protocol. For example, using ammonia as the nucleophile provided access to the NH triazole **31** in 78% isolated yield and the alkene and alkyne containing amines **32** and **33** resulted in the corresponding triazole (85–87%). Incorporation of tertiary amines into the amine substrate was also possible, as exemplified by the diamine **34** (81%). A selection of substituted benzylamines underwent clean conversion to the *N*-benzyl triazole products, where the aromatic ring could tolerate both electron-donating and electron-withdrawing groups, including elaborate handles for further functional groups interconversions (**35**–**37**). Heterocyclic amines (pyridyl-, furfuryl-, azetidyl- and pyrazyl-, **38**–**41**) all underwent cyclisation to poly-heterocyclic systems in excellent yield (68–96%). Aniline (**42**) was also a suitable nucleophilic coupling partner, furnishing the *N*-aryl triazole (74%). Finally, optically active amino-alcohol substrate **43** provided the desired triazole with no erosion in the diastereochemical purity of the product. Whilst under the standard reaction conditions the amino acid derivative **44** gave the triazole product with a substantially reduced e.r., lowering the reaction temperature to 75 °C (18 h) and addition of just 1 equivalent of NEt_3 gave the product with a markedly higher e.r. (98:2) in an excellent 84% isolated yield. It is worth noting that by carrying out the reaction in the presence of NEt_3, many the

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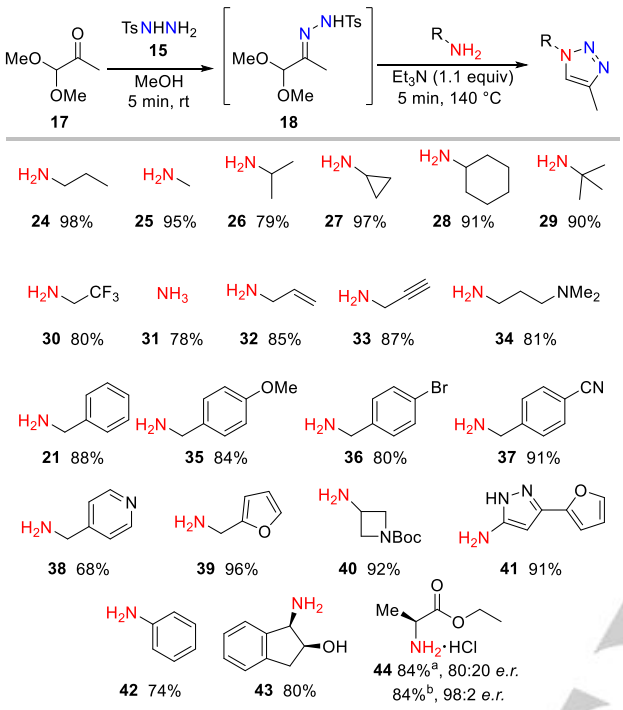
products in Scheme 1 did not require chromatographic purification to afford analytically clean product, greatly increasing the synthetic utility of this efficient transformation.

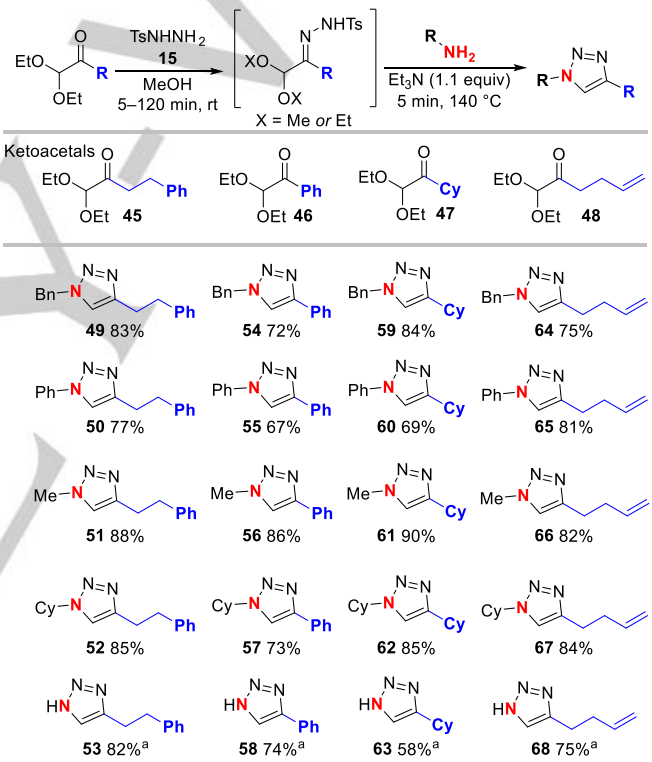
Scheme 1. Scope of primary amine substrate.



[a]2 equiv Et_3N used. [b]Reaction performed in a sealed tube (75 °C, Et_3N 1 equiv, 18 h).

To explore the scope of the α-ketoacetal unit, homo-benzyl, phenyl, cyclohexyl (Cy) and homo-allyl substrates (**45**–**48**) were prepared through a Grignard addition to ethyl 2,2-diethoxyaceatate (See Supporting Information for full experimental details).[15] Each substrate was then reacted with five amines (benzylamine, aniline, methylamine, cyclohexylamine and ammonia) in order to probe both steric and electronic effects on the reaction (Scheme 2). Sterically encumbered α-ketoacetals (phenyl **46** and cyclohexyl **47**) reacted slower with tosylhydrazide **15**, requiring up to 2 h for hydrazone formation, however, the transformation proceeded in quantitative yield to give the expected hydrazone which was treated directly with the appropriate primary amine (1.1 equiv) and NEt_3 (1.1 equiv) before heating at 140 °C for 5 minutes. This array led to all twenty triazoles (**49**–**68**) being isolated in good to excellent yields (58–90%), showing a high level of tolerance of substitution at the 4-position of the triazole. The formation of the triazoles derived from ammonia is of note as the dipolar cycloaddition of an alkyne with inorganic azide (NaN_3) represents a significant synthetic challenge. Further, there are safety concerns due to the energetics of sodium azide and the risk of forming hydrazoic acid[16] highlighting the benefits of this process. The ability to use our 3-component coupling procedure to access this class of heterocycle therefore provides an effective and particularly attractive complementary procedure to the AAC which should be applicable in a process chemistry environment.

Scheme 2. Scope of α-ketoacetal substrate.



[a]2.2 equiv NH_3 used in absence of NEt_3.

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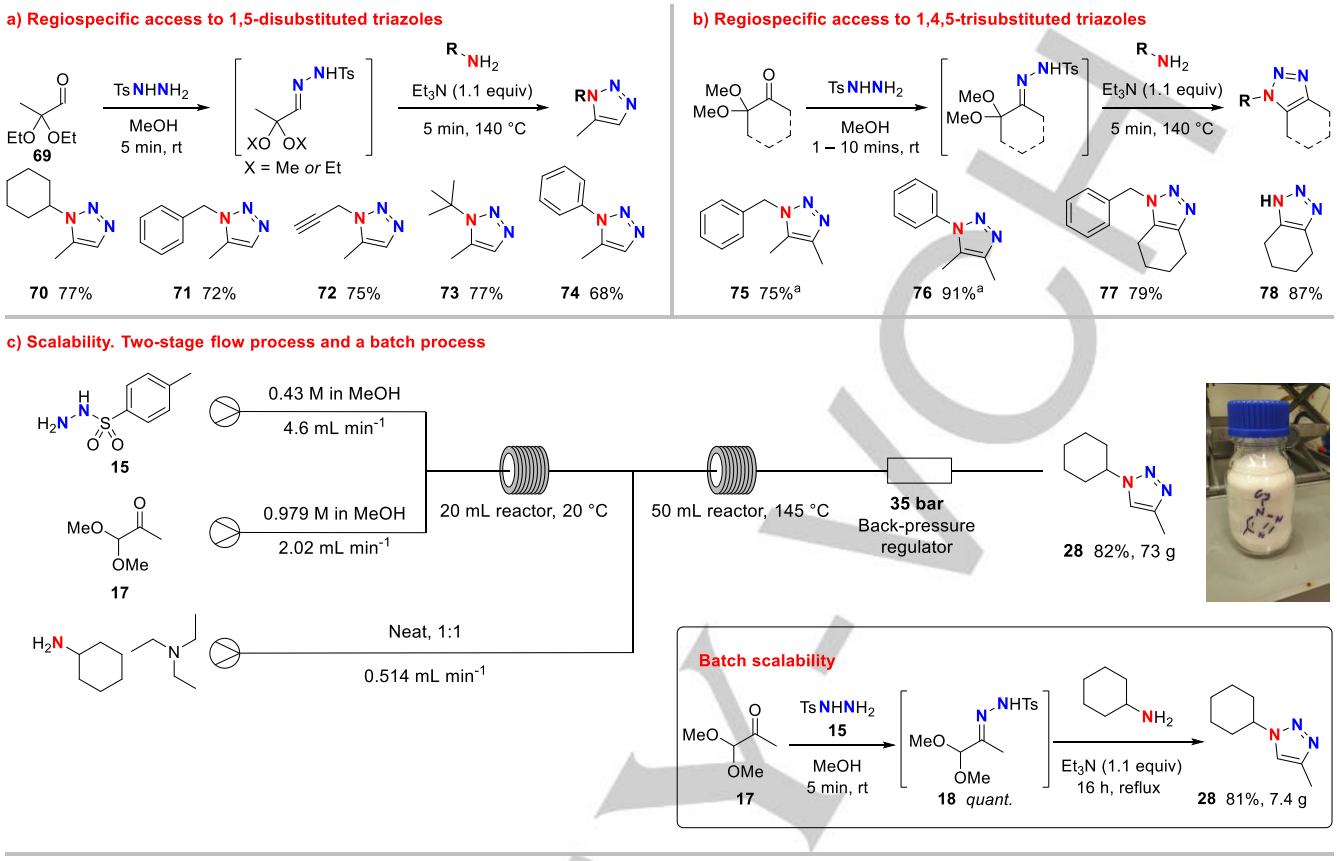

Scheme 3. a) Regiospecific access to 1,5-disusbtituted triazoles. b) Regiospecific access to 1,4,5-trisubstituted triazoles. [a]2 equiv ketoketal used. c) Scalable access to 1,2,3-triazoles using flow or batch reactor. d) Chemoselective 1,2,3-triazole formation.

To further expand the process, we showed that 1,5-disubstituted triazoles could also be prepared using this procedure starting from 2,2-diethoxypropanal **69**, providing a complementary procedure to RuAAC[6] to deliver **70**–**74** in good yield (68–77%, Scheme 3a). This series of results suggests that *α*-ketal aldehydes will prove to be general substrates to access 1,5-disubstituted triazoles with high functional group tolerance under metal-, halogen- and azide-free conditions.

Using α-ketoketals as substrates we were also able to access 1,4,5-trisusbtituted triazoles using this procedure extending the scope of the transformation (Scheme 3b). The triazoles **75** and **76** were isolated in 75% and 91% yields respectively through the reaction of 3,3-dimethoxybutan-2-one under slightly modified conditions. Of note is the fact that cyclic *α*-ketoketals were also suitable substrates providing tetrahydrobenzotriaozles **77** and **78** in 79% and 87% yield respectively. This method is therefore further complementary to AAC chemistry in which cyclohexyne would be the alkyne required to deliver the product. Despite being prepared[17] and used to furnish fused bicyclic triazoles,[18] the use of small (<8 membered) cyclic alkynes remains a significant synthetic challenge within the click chemistry protocol.

To demonstrate the scalability of the procedure, we designed a two-stage flow process for triazole formation (Scheme 3c). Solutions of *N*-tosylhydrazide **15** and α-ketoacetal **17** were reacted in a 20 mL reactor at ambient temperature, before combining with a neat solution of both cyclohexylamine and triethylamine. The solution was then passed through super-heated tubing at 145 °C to allow the cyclisation to occur. From this flow process we isolated 82% of triazole **28** on a 73-gram scale over a processing time of 4.5 hours. This compared favourably with a simple batch-process in which the cyclisation reaction occurred under reflux, isolating 7.4 grams of triazole **28** in an 81% yield after 16 hours. Each of these procedures highlights the utility of the method to access 1,2,3-triazoles from *α*-ketoacetals on a preparative scale.

Finally, to further extend this process we developed a protocol that could be used for the chemoselective reaction of either primary aliphatic amines or primary anilines through simple modification of the reaction conditions (Scheme 3c). Preparation of the hydrazone **18** under standard conditions followed by addition of the amino aniline **79** in the presence of NEt_3 (1 equiv) (140 °C, 5 min) gave the 1,4-triazole **80** (83%) which arose from exclusive reaction of the more nucleophilic aliphatic amine. No indication of a product from reaction through the aniline nitrogen could be detected by examination of the crude reaction mixture by either LCMS or ^{1}H NMR analysis. However, reaction of **18** with the diamine **79** in the presence of TFA (1 equiv, Δ, 18 h) gave the alternative triazole product **81** (87%) where triazole formation had taken place exclusively on the aniline nitrogen.[19] This powerful divergent strategy suggests this method will be applicable to preparation of the triazole of choice through judicious choice of both substrate and additive.

In conclusion, a scalable, metal-, azide- and halogen-free multicomponent reaction to prepare substituted 1,2,3-triazoles has been developed using readily available *α*-ketoacetals, *N*-tosylhydrazide and a primary amine.[20] The procedure shows excellent functional group tolerance and provides access to the substitution pattern of choice in a regiospecific manner. Conducting the reaction in the presence of NEt_3 (1 equiv) allows for the generation of *p*-toluenesulfinic acid as the sole co-product of the transformation which can be removed by aqueous workup. To extend the utility of the reaction further, **28** was prepared under flow or batch reaction conditions highlighting the practical utility and scalability of the method. This work addresses challenges associated with the Sakai reaction by removing the need to isolate a reactive and potentially genotoxic α,α-dichlorohydrazone intermediate and eliminating a problematic bishydrazone co-product. Further, this methodology expands the scope of the process by providing regiospecific access to all substitution patterns of mono-, di- and tri-substituted 1,2,3-triazoles. Chemoselectivity for primary aliphatic amines over anilines has been observed, which has previously been unachievable using α,α-dichloroketones. This selectivity can be reversed by carrying out the reaction in the presence of TFA. Further research into this intriguing method for the preparation of triazoles and its application is ongoing in our laboratory.[21]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,2,3-triazole • azide-free • *α*-ketoacetals • amines • heterocycles

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[14] The mechanism for the formation of **23** remains unclear. However, no precautions were made to degas the solvent or to inert the headspace of the reaction, and so the presence of oxygen could facilitate this oxidative transformation. Moreover, the spectroscopic and analytical data of the isolated species match that of a known sample of **23** and is concurrent with literature

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[19] We believe the TFA acts as a strong Brønsted acid and protonates the more basic aliphatic amine, removing this as a reactive partner. Owing to the acidic reaction conditions, trace quantities of **23** were observed in this reaction which could be removed by column chromatography.

[20] After submission of our work, we became aware that the Sutton group recently detailed a similar strategy to access 1,2,3-triazoles. L. R. Zehnder, J. M. Hawkins, S. C. Sutton. One-Pot, Metal- and Azide-Free Synthesis of 1,2,3-Triazoles from α-Ketoacetals and Amines, *Synlett*, **2019**. DOI: 10.1055/s-0039-1691526

[21] For a potential reaction mechanism, the authors refer the reader to the previous work of Westermann and Hanselmann [11-12] and the additional review article: C. G. S. Lima, A. Ali, S. S. v. Berkel, B. Westermann, M. Paixão, *Chem. Commun,* **2015**, 51, 10784-10796. Based on our current findings, the transformation presented here follows a similar mechanistic pathway, however current research is ongoing within our laboratory to gain a more complete understanding.

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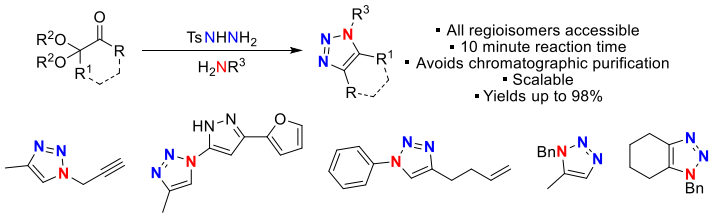

Tri-component tri-azoles: We report a simple and efficient, redox neutral, 3-component synthesis of 1,2,3-triazoles from *α*-ketoacetals, *N*-tosylhydrazide and a primary amine. The method allows access to all triazole substitution patterns, without the requirement for azides, alkynes, halides, transition metals or oxidants.

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