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One-Pot, Metal- and Azide-Free Synthesis of 1,2,3-Triazoles from α-Ketoacetals and Amines

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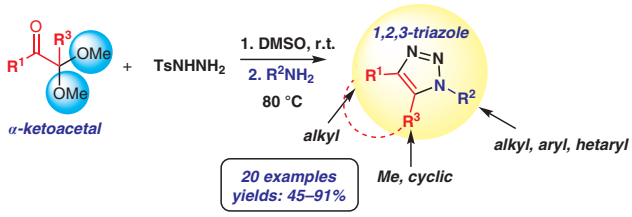

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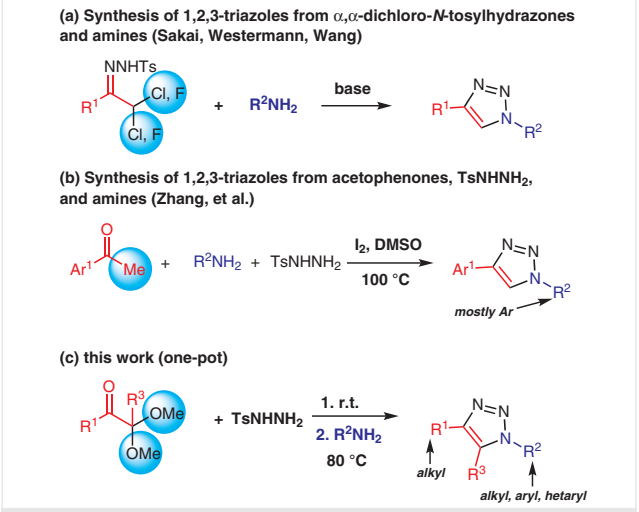
Abstract An efficient one-pot two-step synthesis of 1,4-disubstituted 1,2,3-triazoles from α-ketoacetals and amines is presented. The method does not use metals, azides, or oxidants, and is compatible with a variety of functional groups, including heterocycles, esters, nitriles, and carbamates.

Key words triazoles, ketoacetals, metal-free, azide-free, one-pot synthesis, Sakai reaction

1,2,3-Triazoles are important heterocycles used in pharmaceutical agents, in materials research, in ionic liquids, and as synthetic intermediates.[1] The most popular method for synthesizing 1,2,3-triazoles involves the dipolar cycloaddition between azides and alkynes, first described in the 1960s by Huisgen et al., who used heat to drive the reaction.[2] Since that time, metal-catalyzed cycloadditions between azides and alkynes have been developed to an advanced state now known as click chemistry.[3] The Cu-catalyzed alkyne–azide cycloaddition reaction to form 1,4-disubstituted 1,2,3-triazoles is the most common reaction,[4] whereas Ru- and Ir-catalyzed alkyne–azide cycloaddition reactions are employed for the formation of 1,5-disubstituted 1,2,3-triazoles.[5] Metal-free synthetic methods are desirable to reduce waste-disposal costs and to eliminate the potential for trace transition-metal impurities in commercial products. Moreover, the toxicity and potential thermal hazards of azides make them undesirable intermediates for batch syntheses of 1,2,3-triazoles. There are several methods for constructing 1,2,3-triazoles without the use of azides or transition metals. A review of these methods appeared in 2017, and we refer the reader to this for a compilation of metal- and azide-free triazole work before 2017.[6] The seminal work by Sakai and co-workers in 1986 demonstrated that condensation of α,α-dichloro-*N*-tosylhydrazones with primary amines at room temperature could lead to regioselective formation of 1,4-disubstituted 1,2,3-triazoles (Scheme 1a).[7] Sakai's reaction was found to be highly chemoselective, but was not studied in detail until 2012, when van Berkel et al. examined the mechanism, scope, and limitations of this transformation.[8] One reason for the limited adoption of Sakai's work involves the fragile nature of α,α-dichloro ketones and the limited number of robust methods for preparing these base-sensitive intermediates.[9] Recently, Anthore-Dalion and Zard developed a xanthate functionalization/reductive dexanthylation route to α,α-dichloro ketones.[10] Their work is a rare example of a new method for the synthesis of α,α-dichloro ketones from readily available building blocks.[11] The sensitivity of α,α-dichloro ketones originates from a base-catalyzed Favorskii rearrangement leading to undesired byproducts.



Scheme 1 Synthesis of 1,2,3-triazoles under metal and azide-free conditions

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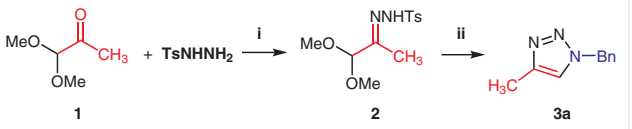
Much of the recent work on azide-free 1,2,3-triazole synthesis has moved away from α,α-dichlorohydrazones. For example, Zhang and co-workers reported a 1,2,3-triazole synthesis from *N*-tosylhydrazones and amines by using stoichiometric $Cu(OAc)_2$ and, in work closer to ours, the same group used I_2 and $TsNHNH_2$ in DMSO to oxidize methyl ketones flanked by aryl groups to α-oxidized tosylhydrazones that underwent a similar cyclization to that discussed here (Scheme 1b).[12] The use of alkyl amines in Zhang's work[12b] led to low yields of product and required an extra oxidant (TBHP or Oxone) in addition to I_2. Ji and co-workers reported an I_2/TBHP-mediated synthesis of 1,2,3-triazole by using acetophenone-derived *N*-tosylhydrazones and anilines, as well as α-chlorocarbonyl-derived *N*-tosylhydrazones and anilines under aerobic conditions.[13] Wang and co-workers used α,α-difluoro-*N*-tosylhydrazones and amines to prepare 1,2,3-triazoles through treatment with *t*-BuOLi in toluene at 100 °C.[14] The strong base and high-temperature conditions for the α,α-difluoro reaction appeared to limit the substrate scope to nonfunctionalized alkyl, aryl, or pyridyl groups. Other metal-free triazole methods similar to the current work published since 2017 include (a) a metal-free cascade [4+1] cyclization to give 4-aryl-NH-1,2,3-triazoles from *N*-tosylhydrazones and sodium azide,[15] (b) a synthesis of 5-thiolated 1,2,3-triazoles from β-thioenaminones through a diazo-transfer reaction under aqueous conditions,[16] (c) reactions of α-haloacroleins with azides to give formyl triazoles,[17] (d) a catalyst-free route to 4-acyl-NH-1,2,3-triazoles by water-mediated cycloaddition reactions of enaminones and tosyl azide,[18] (e) [3+2] annulation of alkyl propiolates for the synthesis of 1,5- and 1,4-disubstituted 1,2,3-triazoles containing an ester group by using tosyl azide or tosylhydrazine as the nitrogen source,[19] and (f) TBAI- or KI-promoted oxidative coupling of enamines containing electron-withdrawing groups with *N*-tosylhydrazine to prepare triazoles.[20] Of the six metal-free triazole methods published since 2017, five used some form of azide. We sought to expand upon Sakai's original work, because it had the benefits of being mild, regiospecific, and metal-, azide-, and oxidant-free, and it gave generally high yields. We also wanted a reaction that would tolerate both alkyl and aryl groups at the 1- and 5-positions of the triazole to broaden the scope of existing methods. To this end, our strategy was to employ a less-sensitive *N*-tosylhydrazone intermediate at the same oxidation state as the α,α-dichloro-*N*-tosylhydrazone. Our approach involved replacing the α,α-dichloro functional group with an α,α-dimethoxy or α,α-diethoxy acetal (Scheme 1c). The expected stability of the α-ketoacetals to synthetic manipulation and the significant number of known methods for preparing them[21] inspired the research presented here.

In our first attempt to test the feasibility of this approach, we used the commercial α-ketoacetal **1**. Treatment of **1** with one equivalent of 4-methylbenzenesulfonohydrazide ($TsNHNH_2$) in DMSO afforded hydrazone **2** in 89% yield after precipitation of the white solid from water. Treatment of **2** with benzylamine in DMSO at 80 °C for four hours afforded the desired triazole **3** in 59% yield for an overall two-step yield of 53%.

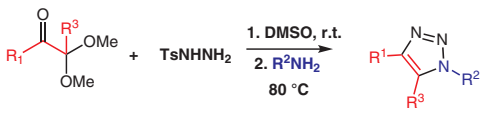
Having established that the reaction sequence shown in Scheme 2 works, we sought to simplify the procedure by preparing the *N*-tosylhydrazone and the 1,2,3-triazole in the same reaction vessel. Telescoping the reaction sequence of Scheme 2 afforded an 87% yield of **3a**, supporting the expectation that, in most cases, yields from the two-step one-pot method are at least equivalent to those from the stepwise approach, if not better.



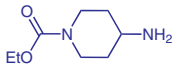
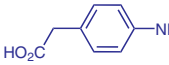
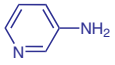
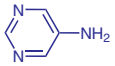
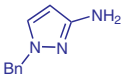
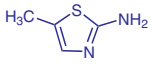
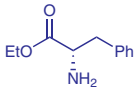
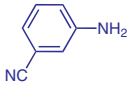
Scheme 2 Two-step process using α-keto acetal **1**. *Reagents and conditions*: (i) DMSO, r.t., 89%; (ii) $BnNH_2$, DMSO, 80 °C, 4 h (59% two steps; 87%, one-pot).

To establish the scope and limitations of the reaction, we coupled a variety of primary amines and α-ketoacetals. Alkyl amines, anilines, and heterocyclic amines worked well giving yields of 55–91% from the telescoped procedure (Table 1).[22] We observed that both dimethoxy and diethoxy α-ketoacetals work in this transformation, with the dimethoxy α-ketoacetal **1** giving a slightly better yield of **3a** (87% as against 77% the diethoxy analogue). We also noted that methyl substitution on the quaternary acetal carbon (R^3 in Table 1) works well, leading to trisubstituted 1,2,3-triazoles with a methyl group at the 5-position (Table 1, entries 5 and 15). Weakly nucleophilic anilines and hetaryl amines gave the corresponding products in yields of 55–70% (entries 7–11, 13, 14). Functional groups, including esters, carbamates, carboxylic acids, and nitriles, were tolerated under the mild conditions employed. A comparison of the α-ketoacetal approach with the α,α-dichloro-*N*-tosylhydrazone method is shown in entry 9; we obtained a similar yield (64%) to that achieved by van Berkel et al. (59%).[8] Chirality was maintained in the α-amino ester example under the mild reaction conditions (entry 16).

Table 1 Reaction Scope Using Various Amines and α-Ketoacetals[a]

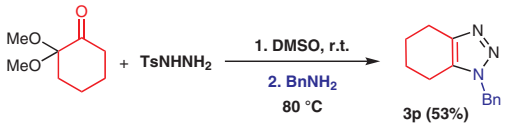


Entry	Product	R^1	R^2NH_2	R^3	Yield[b] (%)
1	**3a**	Me	$BnNH_2$	H	87
2	**3b**	Me	$Ph(CH_2)_2NH_2$	H	56
3	**3c**	Me	Ph_2CHNH_2	H	80

Entry	Product	R^1	R^2NH_2	R^3	Yield[b] (%)
4	**3d**	Me		H	61
5	**3e**	Me	Ph_2CHNH_2	Me	65
6	**3f**	Me	t-$BuO_2CCH_2NH_2$	H	75
7	**3g**	Me	$PhNH_2$	H	70
8	**3h**	Me	4-$MeO_2CC_6H_4NH_2$	H	55
9[c]	**3i**	Me		H	64
10	**3j**	Me		H	62
11	**3k**	Me		H	60
12	**3l**	H	$BnNH_2$	H	45
13	**3m**	Me		H	63
14	**3n**	Me		H	56
15	**3o**	Me	$BnNH_2$	Me	91
16[d]	**3q**	Me		H	60[e]
17	**3r**	Me		H	75
18	**3s**	Me		H	72

[a] Reaction conditions: (i) DMSO, $TsNHNH_2$ (1.0 equiv), r.t., 1 h; (ii) amine, 80 °C, 4 h.
[b] Isolated yield.
[c] See ref. 8 for the Sakai reaction on this substrate.
[d] The HCl salt of the amine was used with one equivalent of pyridine.
[e] 95% ee.

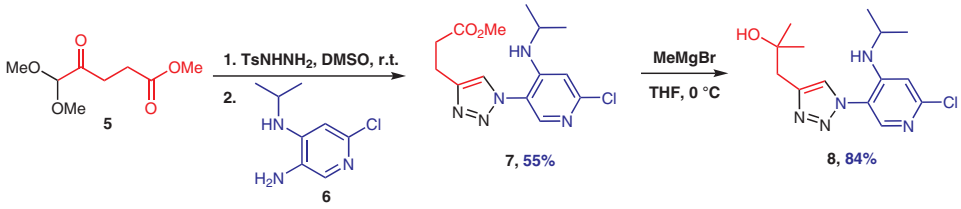
A cyclic example, 2,2-dimethoxycyclohexan-1-one, was surveyed to determine if the scope could be extended to the formation of bicyclic products. Indeed, a 53% yield of the 5,6-fused heterocycle **3p** was obtained in one step from commercial starting materials (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) DMSO, r.t., 30 min (hydrazone formation not observed); (ii) $BnNH_2$, DMSO, 80 °C, 4 h (53%).

Finally, a tangible application of this reaction in the preparation of an intermediate leading to the IRAK4 inhibitor BMS-986236[23] was examined to highlight the advantages of this azide-free method (Scheme 4). The first-generation synthesis of BMS-986236 used an energetic azide intermediate, necessitating a second-generation synthesis for scale-up that used a less-energetic hetaryl azide. Heating a mixture of α-ketoacetal **5**[24] with $TsNHNH_2$ and aniline **6** at 80 °C for six hours afforded a 51% yield of triazole **7**.[25] In this reaction, mixing all three components together at the beginning of the reaction resulted in slightly higher yields compared with the usual stepwise formation of the *N*-tosylhydrazone at room temperature followed by addition of the amine and then heating to 80 °C. It is conceivable that the *N*-tosylhydrazone of **5** has a short half-life, even at room temperature, and immediate consumption leading to triazole **7** is beneficial to the yield. Conversion of **7** into **8** was accomplished by inverse addition of the ester to MeMgBr in THF at 0 °C, affording the penultimate intermediate leading to BMS-986236. The ^1H NMR of **8** generated in this way was identical to the reported spectrum.

In conclusion, this 1,2,3-triazole synthesis represents a convenient modification of the Sakai method and is expected to expand the scope of the reaction by avoiding the use of base-sensitive α,α-dichloro ketones.[24] The scope of the present reaction extends to alkyl, aryl, or hetaryl groups at the 1-position and to alkyl groups at the 4-position. 2,2-Diethoxyacetophenone was investigated (not shown), but afforded an average of 30% yield after three replicates. Because the acetophenone scope is covered broadly by the other methods cited in the introduction, we did not focus our attention on the optimization of the acetophenone-derived α-ketoacetals. The orthogonal scope of the current method complements previous work in the acetophenone space. Finally, a scaled-up method not involving an azide (or a metal) might offer advantages for the synthesis of 1,2,3-triazoles in terms of mitigation of thermal hazards



Scheme 4 Azide-free synthesis of **8**, leading to BMS-986236

and the elimination of trace metals. However, it is important to note that hydrazides, hydrazones, 1,2,3-triazoles, and DMSO are known to have either low decomposition onsets, high decomposition energies, or both. The safety of reactions involving low-onset or high-energy compounds needs to be evaluated on a case-by-case basis.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691526.

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(22) **Methyl 4-(4-Methyl-1*H*-1,2,3-triazol-1-yl)benzoate (3h); Typical Procedure**
TsNHNH$_2$ (308 mg, 1.65 mmol) was added to a solution of 1,1-dimethoxypropan-2-one (195 mg, 1.65 mmol) in DMSO (2 mL), and the mixture was stirred for 1 h at r.t. Methyl 4-aminobenzoate (262 mg, 1.74 mmol) was then added and the mixture was heated at 80 °C for 4 h, then cooled. The solution was filtered and purified by supercritical fluid chromatography (Princeton HA-Morpholine column) to give a white solid; yield: 198 mg (55%).
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (s, 1 H), 8.19–8.10 (m, 2 H), 8.08–7.98 (m, 2 H), 3.89 (s, 3 H), 2.34 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.3, 143.6, 139.9, 130.9, 128.9, 120.5, 119.4, 52.3, 10.4. HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{11}H_{12}N_3O_2$: 218.0924; found: 218.0930.
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(25) **Methyl 3-{1-[6-Chloro-4-(isopropylamino)pyridin-3-yl]-1*H*-1,2,3-triazol-4-yl}propanoate (7)**
To a solution of TsNHNH$_2$ (98 mg, 0.53 mmol) were added ester **5** (100 mg, 0.55 mmol), prepared according to ref. 24, and diamine **6** (100 mg, 0.53 mmol) in DMSO (1 mL), and the mixture was heated at 80 °C for 6 h, then cooled. The resulting solution was purified by reverse-phase chromatography [Teledyne Isco ACCQPrep; Luna Omega 5µm Polar C18 column (250 × 30 mm), gradient elution: H_2O–HOAc/MeCN]. The pure fractions were combined, and MeCN was removed by evaporation under reduced pressure. The resulting aqueous mixture was frozen and lyophilized to give a white solid; yield: 91 mg (55%).
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.30 (s, 1 H), 8.05 (s, 1 H), 6.91 (s, 1 H), 6.41 (br d, *J* = 7.9 Hz, 1 H), 3.86–3.77 (m, 1 H), 3.62 (s, 3 H), 3.03–2.96 (m, 2 H), 2.80–2.73 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.4, 151.3, 148.2, 145.9, 144.5, 123.5, 119.3, 105.2, 51.4, 43.4, 32.4, 21.6, 20.5. HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{14}H_{19}ClN_5O_2$: 324.1222; found: 324.1223.