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An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted 4-Thio-1,2,3-triazoles and 1,5-Disubstituted 1,2,3-Triazoles

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Abstract: Organocatalytic azide–ketone [3+2] cycloaddition (OrgAKC) of a variety of 1-aryl-2-(arylthio)ethanones and 1-alkyl-2-(alkylthio)ethanones with different aryl or alkyl azides is reported in dimethyl sulfoxide or solvent-free under ambient conditions to furnish 1,5-disubstituted 4-thio-1,2,3-triazoles in a regiospecific manner, which are further converted into useful 1,5-disubstituted 1,2,3-triazoles by treatment with Raney Ni at 25 °C for 1–3 h. Notable features of the OrgAKC reaction include high rate and selectivity, solvent-free conditions, easily available substrates and catalysts, a wide range of synthetic and medicinal applications, and excellent yields generating a vast library of triazoles.

1,4-/1,5-Disubstituted 1,2,3-triazoles and 1,4,5-trisubstituted 1,2,3-triazoles have garnered much interest as peptide bond isosteres and also as an important family of heterocycles, which exhibit a vast spectrum of properties and applications and are widely used in pharmaceuticals.[1] In particular, 1,2,3-triazoles containing 4-thiomethyl or 5-thio compounds and 1,5-disubstituted 1,2,3-triazoles have found widespread medicinal application in anticancer drugs, antifungal agents, antibacterial drugs, anti-inflammatory drugs, mPGES-1 inhibitors, bioorthogonal probes, and also as human dUTPase inhibitors (Figure 1).[2] With these applications, the development of more general and green protocols for the synthesis of their analogues is of significant interest.[3]

The regioselective copper-catalyzed azide–alkyne [3+2] cycloaddition (CuAAC) reaction, reported by the groups of Sharpless and Meldal in 2002, led to a huge expansion of interest in 1,4-disubstituted 1,2,3-triazoles.[4] After the discovery of this click reaction, many researchers entered this field and made significant contributions in terms of structural evolution, reaction development, and applications in the chemical and biological sciences. Novel reaction discoveries in this field have included, zinc-, ruthenium-, iridium-, and samarium-catalyzed azide–alkyne [3+2] cycloadditions,[5] strain-promoted azide–alkyne [3+2] cycloaddition (SPAAC),[6] base-promoted azide–alkyne [3+2] cycloaddition,[7] azide–bromomagnesium acetylide [3+2] cycloaddition,[8] organocatalytic enamine- or enolate-mediated azide–carbonyl [3+2] cycloaddition,[9,10] copper- or iodine/*tert*-butyl peroxybenzoate-promoted reaction of *N*-tosylhydrazones with anilines,[11] iodine-promoted three-component reaction of *N*-tosylhydrazones, arylketones and anilines,[12] and electronically controlled active olefin–azide [3+2] cycloaddition.[13] Many of these reactions are suitable to synthesize a variety of 1,2,3-triazoles, based on the availability of substrates and catalysts.

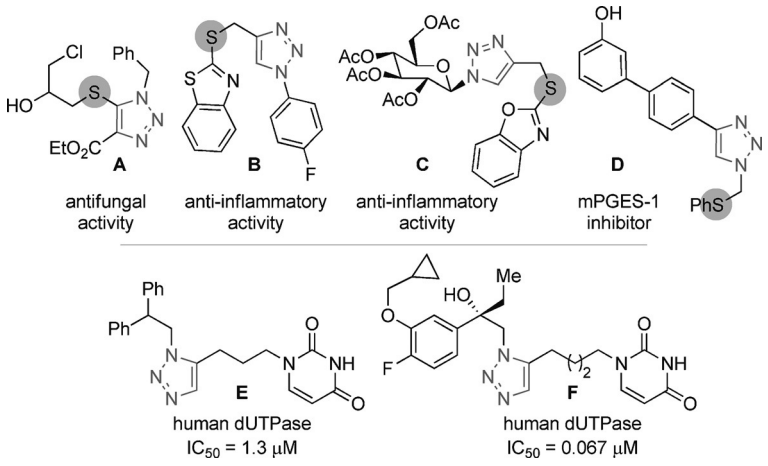

Figure 1. Potential applications based on the 1,2,3-triazoles.

In search of medicinally important 1,2,3-triazoles, we thought of synthesizing 1,5-disubstituted 4-thio-1,2,3-triazoles,[2] as their analogues have played significant roles in pharmaceutical and biological chemistry (Figure 1).[2] Although base-promoted S_NAr reaction of 5-fluoro-1,2,3-triazoles with alkyl thiols (Scheme 1 a)[14] and iridium-catalyzed [3+2] cycloaddition of thioalkynes with aryl azides (Scheme 1 b)[15] have both been reported as protocols to furnish 5-thio-1,2,3-triazoles through metal catalysis, there is, to our knowledge, no reaction available to prepare 4-thio-1,2,3-triazoles. Herein, we report a general, rapid, and operationally simple organocatalytic azide–ketone [3+2] cycloaddition (OrgAKC) reaction for the

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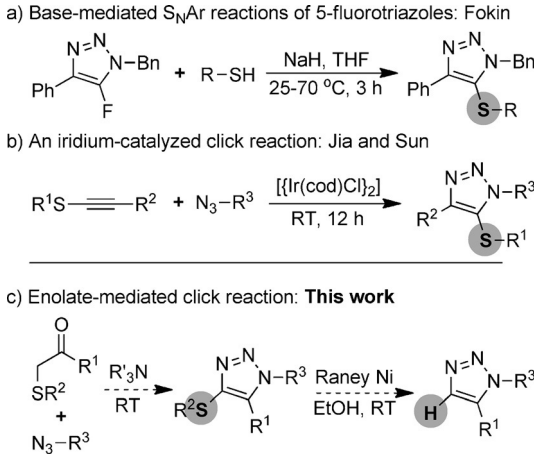


Scheme 1. Design for the enolate-mediated OrgAKC reaction.

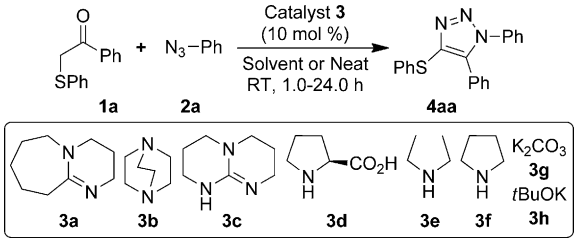
chemo- and regiospecific high-yielding synthesis of 1,5-disubstituted 4-thio-1,2,3-triazoles from aryl or alkyl azides and 1-aryl-2-(arylthio)ethanones or 1-alkyl-2-(alkylthio)ethanones (Scheme 1c). One very important benefit of this method is that useful 1,5-disubstituted 1,2,3-triazoles could also be easily synthesized from the common intermediate, 1,5-disubstituted 4-thio-1,2,3-triazoles, through desulfurization with Raney Ni at room temperature (Scheme 1c).

Based on the above proposal, we first chose 1-phenyl-2-(phenylthio)ethanone **1a** and phenyl azide **2a** as substrates for the reaction optimization. We commenced optimization of the OrgAKC reaction by using commercially available 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **3a** (pK_a of conjugate acid in DMSO = 12) as the organocatalyst for the click reaction of 1-phenyl-2-(phenylthio)ethanone **1a** (pK_a of methylene C–H bonds in DMSO = 16.9) with 1.2–1.5 equivalents of phenyl azide **2a** (Table 1). The click reaction of ketone **1a** with 1.2 equivalents of **2a** in DMSO, catalyzed by 10 mol% of **3a** at 25 °C for 2.5 h furnished the expected 4-thio-1,2,3-triazole **4aa** as a single regioisomer in moderate yield (Table 1, entry 1). The same reaction over an extended time (6 h) at 25 °C furnished **4aa** in 85% yield (Table 1, entry 2). When the amount of azide **2a** was increased from 1.2 to 1.5 equivalents, the same reaction over 6 h furnished the **4aa** in 90% yield (Table 1, entry 3). At a reaction temperature of 50 °C, the same reaction of **1a** with 1.5 equivalents of **2a** furnished **4aa** in 90% yield within 1 h (Table 1, entry 4). To investigate whether the DBU-promoted OrgAKC reaction is solvent dependent, we carried out the click reaction in various other solvent systems, including aqueous dimethyl sulfoxide [DMSO + H_2O (7:3 v/v)], DMF, CH_3CN, $CHCl_3$, and EtOH. However, we obtained the click product **4aa** in decreased yields of 50%, 76%, 42%, < 3%, and < 5%, respectively, and longer reaction times of up to 24 h were required, except in DMF (Table 1, entries 5–9). These results clearly support our hypothesis of the involvement of reactive in situ enolate formation from **1a** with **3a** during the course of the reaction.

To further investigate the reactivity of amine and non-amine catalysts on OrgAKC reaction, we carried out the click reaction with 10 mol% of various catalysts, including DABCO (**3b**), triazabicyclodecene (**3c**), proline (**3d**), diethylamine (**3e**), pyrrolidine (**3f**), K_2CO_3 (**3g**), and *t*BuOK (**3h**) in DMSO at 25 °C. However, with catalysts **3c** and **3e**, we obtained the **4aa** in only 37% and 22% yield, respectively, and with the other catalysts conversions of 0–< 5% were obtained (Table 1, entries 10–16). To make this click reaction greener, we tested the reaction under solvent-free conditions. Pleasingly, the solvent-free reaction of **1a** (0.5 mmol, 114 mg) and **2a** (0.75 mmol, 88.6 μL) with **3a** (0.05 mmol, 7.5 μL) at 25–50 °C for 1.5 h furnished **4aa** in 85–90% yields (Table 1, entries 17 and 18). In these reactions, the phenylthio (Ph–S) group was electronically responsible for inducing the acidity of C–H bonds in **1a**, as proven by the control experiments. No click reaction was observed between acetophenone (PhS = H) and phenyl azide through enolate or enamine formation catalyzed by of amines or amino acids (see the Supporting Information, Table S1). We therefore identified the optimized conditions as 25–50 °C in DMSO or solvent-free, catalyzed by 10 mol% of DBU **3a**, which furnished the single isomer **4aa** in 90% yield from **1a** and **2a** (Table 1, entries 3, 4, and 18).

With the optimized conditions in hand, the scope and the generality of the DBU-catalyzed OrgAKC reactions were investigated. A variety of substituted aryl and alkyl azides **2b**–**p** reacted with ketone **1a** catalyzed by 10 mol% of **3a** at 25 °C both in solvent-free conditions and in DMSO for 0.75–6 h (Table 2).

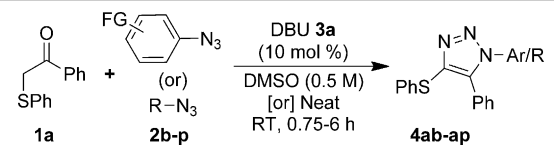
Table 1. Reaction optimization.[a]



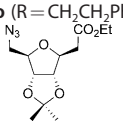
Entry	Catalyst **3**	Solvent	Azide **2a** [equiv]	*t* [h]	Yield **4aa** [%][b]
1	**3a**	DMSO	1.2	2.5	65
2	**3a**	DMSO	1.2	6.0	85
3	**3a**	**DMSO**	**1.5**	**6.0**	**90**
4[c]	**3a**	**DMSO**	**1.5**	**1.0**	**90**
5[d]	**3a**	DMSO + H_2O	1.5	24.0	50
6	**3a**	DMF	1.5	2.0	76
7	**3a**	CH_3CN	1.5	17.0	42
8[e]	**3a**	$CHCl_3$	1.5	24.0	< 3
9[e]	**3a**	EtOH	1.5	24.0	< 5
10[e]	**3b**	DMSO	1.5	24.0	< 3
11	**3c**	DMSO	1.5	24.0	37
12[e]	**3d**	DMSO	1.5	24.0	–
13	**3e**	DMSO	1.5	24.0	22
14[e]	**3f**	DMSO	1.5	24.0	–
15[e]	**3g**	DMSO	1.5	24.0	< 5
16[e]	**3h**	DMSO	1.5	6.5	< 5
17	**3a**	**solvent-free**	**1.5**	**1.5**	**85**
18[c]	**3a**	**solvent-free**	**1.5**	**1.5**	**90**

[a] Reactions were carried out in solvent (0.5 M) or solvent-free with **1a** (0.5 mmol) and **2a** (1.2–1.5 equiv) in the presence of 10 mol% of catalyst **3**; [b] yields refer to product isolated by column chromatography; [c] *T* = 50 °C; [d] DMSO + H_2O (7:3 v/v) was used as solvent; [e] starting materials **1a** and **2a** were recovered.

Table 2. Azide scope.[a]



1a 2b-p 4ab-ap

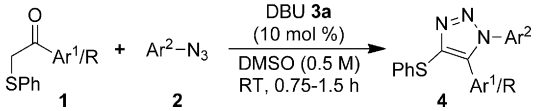
Entry	$Ar–N_3$ or $R–N_3$ **2**	Yield **4** [%][b,c]
1	**2b** (FG = 4-NO_2)	**4ab**: 93 (85)
2	**2c** (FG = 4-CO_2Et)	**4ac**: 90 (90)
3	**2d** (FG = 4-CN)	**4ad**: 93 (85)
4	**2e** (FG = 4-CF_3)	**4ae**: 97 (85)
5	**2f** (FG = 4-CHO)	**4af**: 87 (81)
6	**2g** (FG = 4-F)	**4ag**: 95 (90)
7	**2h** (FG = 4-Cl)	**4ah**: 95 (88)
8	**2i** (FG = 3-Cl)	**4ai**: 96 (85)
9	**2j** (FG = 4-Br)	**4aj**: 88 (92)
10[d]	**2k** (FG = 4-Me)	**4ak**: 90 (87)
11[d]	**2l** (FG = 4-OMe)	**4al**: 55 (72)
12[e]	**2m** (FG = (*R*)-4-CH_3COCH_2CHOH)	**4am**: 65 (63)
13[d,f]	**2n** (R = CH_2Ph)	**4an**: – (65)
14[d,f]	**2o** (R = CH_2CH_2Ph)	**4ao**: – (40)
15[d,f,g]	**2p** 	**4ap**: – (60)

[a] Reactions were carried out in DMSO (0.5 M) or solvent-free with **1a** (0.5 mmol) and **2b–p** (1.5 equiv) in the presence of 10 mol% of **3a**; [b] yields refer to product isolated by column chromatography; [c] values in parentheses refer to the yields of the solvent-free reaction; [d] T = 50 °C; [e] *ee* of **2m** is 75.9% and that of **4am** is 75.7%, based on the chiral HPLC analysis; [f] reaction performed in solvent-free conditions only; [g] t = 24 h.

The aryl azides **2b–j**, with substituents including NO_2, CO_2Et, CN, CF_3, CHO, F, Cl, and Br, furnished the expected 4-thio-1,2,3-triazoles **4ab–aj** in excellent yields within 0.75 h in both sets of conditions, without showing much difference (Table 2, entries 1–9). Reaction rates and yields of the 4-thio-1,2,3-triazoles **4ab–aj** were increased by electron-withdrawing substituents at the *para* position of **2**, but rate and yields slightly decreased with alkyl and electron-donating substituents. For example, the DBU-catalyzed OrgAKC reaction of the aryl azides 4-$CH_3C_6H_4N_3$ (**2k**) and 4-$OCH_3C_6H_4N_3$ (**2l**) with ketone **1a** in DMSO at 25 °C took longer time (6 h) for lower yields (65% and 25%, respectively); but the same reactions at 50 °C for 2.0 h furnished the 4-thio-1,2,3-triazoles **4ak** and **4al** in 90% and 55% yields, respectively (Table 2, entries 10 and 11). Similar results were obtained with **2k** and **2l** in solvent-free conditions, but the yield of **4al** was increased compared to that in DMSO. The reaction of **1a** with chiral (*R*)-**2m** having 75.9% *ee*, catalyzed by 10 mol% of **3a**, furnished (*R*)-**4am** in 65% yield with similar (75.7%) *ee* (Table 2, entry 12). Surprisingly, no reaction was observed for the **3a**-catalyzed OrgAKC reaction of **1a** with alkyl and sugar azides **2n–p** in DMSO at 25–65 °C for 24 h, but the same reaction under solvent-free conditions at 50 °C for 3, 6, and 24 h furnished **4an, 4ao**, and **4ap** in 65%, 40%, and 60% yields, respectively (Table 2, entries 13–15). The longer reaction time (24 h) required for the OrgAKC reaction of **1a** with azido sugar **2p** may be due to the highly viscous nature of the reaction mixture because of the polar functional groups. 1,2,3-Triazole formation from alkyl or sugar azides is a useful reaction in click chemistry,[16] which highlights the importance of the OrgAKC reaction in glycoscience.

Having elucidated the solvent effects and the electronic and steric factors of aryl, alkyl, and sugar azides **2** in the [3+2] cycloaddition reaction, we further investigated the reaction scope with different 1-aryl-2-(phenylthio)ethanones **1b–n** and 1-(phenylthio)propan-2-one **1o** in the OrgAKC reaction with $C_6H_5N_3$ (**2a**), 4-$CF_3C_6H_4N_3$ (**2e**), and 4-$FC_6H_4N_3$ (**2g**) under both sets of conditions (Table 3). In this reaction, 1-aryl-2-(phenylthio)ethanones **1b–n**, containing functional groups including 4-NO_2, 3-NO_2, 4-CN, 4-CF_3, 4-F, 4-Cl, 4-Br, 4-I, 4-OMe, 4-Me, 2-naphthyl, 4-phenyl, and heteroaryl, were used as substrates for the organocatalytic synthesis of single isomers of 1,4,5-trisubstituted 4-thio-1,2,3-triazoles **4be–ne**, **4fa**, and **4gg** in good to excellent yields within 0.75–1.5 h (Table 3, entries 1–15). In a similar manner, the OrgAKC reaction of 1-(phenylthio)propan-2-one **1o** with aryl azides **2a** and **2e** catalyzed by **3a** at RT for 0.75 h in DMSO furnished **4oa** and **4oe** in 65% and 80% yields, respectively (Table 3, entries 16 and 17). The OrgAKC reactions of **1j**, **1n**, and **1o** with **2e** or **2a** in DMSO gave click products **4je**, **4ne**, and **4oa** in 70%, 62% and 65% yields, whereas the same reactions under solvent-free conditions also furnished the products in moderate yields (66%, 56% and 61%, respectively; Table 3, entries 11, 15, and 16). The results in Table 3 demonstrate the broad scope of this methodology, covering a structurally diverse group of 1-aryl-2-

Table 3. Ketone scope: α-(Phenylthio)ketones.[a]



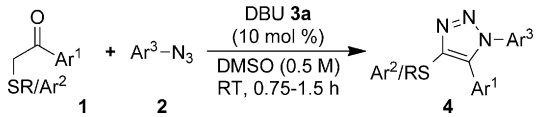
Entry	**1** (Ar^1 or R)	$Ar^2–N_3$ **2**	Yield **4** [%][b]
1	**1b** (Ar^1 = 4-$NO_2C_6H_4$)	**2e**	95 (**4be**)
2	**1c** (Ar^1 = 3-$NO_2C_6H_4$)	**2e**	91 (**4ce**)
3	**1d** (Ar^1 = 4-CNC_6H_4)	**2e**	90 (**4de**)
4	**1e** (Ar^1 = 4-$CF_3C_6H_4$)	**2e**	85 (**4ee**)
5	**1f** (Ar^1 = 4-FC_6H_4)	**2a**	95 (**4fa**)
6	**1f** (Ar^1 = 4-FC_6H_4)	**2e**	85 (**4fe**)
7	**1g** (Ar^1 = 4-ClC_6H_4)	**2g**	85 (**4gg**)
8	**1g** (Ar^1 = 4-ClC_6H_4)	**2e**	90 (**4ge**)
9	**1h** (Ar^1 = 4-BrC_6H_4)	**2e**	83 (**4he**)
10	**1i** (Ar^1 = 4-IC_6H_4)	**2e**	82 (**4ie**)
11[c]	**1j** (Ar^1 = 4-$OMeC_6H_4$)	**2e**	70 (**4je**)
12	**1k** (Ar^1 = 4-MeC_6H_4)	**2e**	93 (**4ke**)
13	**1l** (Ar^1 = 2-Naphthyl)	**2e**	90 (**4le**)
14	**1m** (Ar^1 = 4-PhC_6H_4)	**2e**	92 (**4me**)
15[c]	**1n** (Ar^1 = Furan-2-yl)	**2e**	62 (**4ne**)
16[c]	**1o** (R = Me)	**2a**	65 (**4oa**)
17	**1o** (R = Me)	**2e**	80 (**4oe**)

[a] Reactions were carried out in DMSO (0.5 M) with **1b–o** (0.5 mmol) and **2** (1.5 equiv) in the presence of 10 mol% of **3a**; [b] yields refer to product isolated by column chromatography; [c] yields of 66% (**4je**), 56% (**4ne**), and 61% (**4oa**) were obtained through solvent-free reaction of **1j**, **1n**, and **1o** with **2e** or **2a** at RT for 1 h.

(phenylthio)ethanones **1b–n**, 1-(phenylthio)propan-2-one **1o**, and aryl azides **2a**, **2e**, and **2g**. Many of the OrgAKC product **4** yields obtained compared very well to iridium-catalyzed azide–thioalkyne [3+2] cycloaddition[5] (Table 3 and Scheme 1). The structure and the regiochemistry of the OrgAKC products **4aa–ap/4ba–oa/4be–oe/4gg** were confirmed by NMR spectroscopy. Moreover, the structure of **4je** was definitively established X-ray structure analysis (see the Supporting Information, Figure S1).[17]

To further investigate the importance of the alkyl/aryl substitution on the sulfur atom to the acidity of the α-methylene of 1-aryl-2-(arylthio)ethanones and 1-aryl-2-(alkylthio)ethanones **1p–w** in the OrgAKC reaction, we chose the highly functionalized ketones **1p–w**, which have low or high α-methylene acidity compared to 1-aryl-2-(phenylthio)ethanones **1a–o** (Table 4).

Table 4. Ketone scope: Other α-(arylthio)ketones[a]



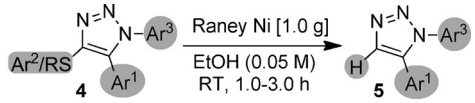
1 2 4

Entry	**1** (R, Ar^1, or Ar^2)	Ar^3–N_3 **2**	Yield **4** [%][b]
1	**1p** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-FC_6H_4)	**2e**	87 (**4pe**)
2	**1q** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-ClC_6H_4)	**2e**	85 (**4qe**)
3	**1r** (Ar^1 = 4-PhC_6H_4; Ar^2 = 4-ClC_6H_4)	**2e**	85 (**4re**)
4	**1s** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-BrC_6H_4)	**2e**	85 (**4se**)
5	**1t** (Ar^1 = 4-PhC_6H_4; R = octyl)	**2e**	92 (**4te**)
6	**1u** (Ar^1 = 4-FC_6H_4; R = decyl)	**2e**	92 (**4ue**)
7	**1v** (Ar^1 = 4-MeC_6H_4; Ar^2 = 4-$CF_3C_6H_4$)	**2e**	92 (**4ve**)
8	**1w** (Ar^1 = C_6H_5; R = $CH_2C_6H_5$)	**2a**	87 (**4wa**)

[a] Reactions were carried out in DMSO (0.5 M) with **1p–w** (0.5 mmol) and **2** (1.5 equiv) in the presence of **3a** (10 mol%); [b] yields refer to product isolated by column chromatography;

The reaction of 1-[(1,1′-biphenyl)-4-yl]-2-[(2-fluorophenyl)thio]-ethanone (**1p**) with 4-$CF_3C_6H_4N_3$ (**2e**) catalyzed by DBU at 25 °C for 1.5 h furnished the expected 4-thio-1,2,3-triazole **4pe** in 87% yield without showing the effects of steric or electronic factors (Table 4, entry 1). In a similar manner, the reaction of 2-chlorophenylthioethanone (**1q**), 4-chlorophenylthioethanone (**1r**), and 2-bromophenylthioethanone (**1s**) with 4-$CF_3C_6H_4N_3$ (**2e**) catalyzed by DBU at 25 °C for 1.5 h furnished the 4-thio-1,2,3-triazoles **4qe–se**, each in 85% yield (Table 4, entries 2–4). We also utilized three examples of 1-aryl-2-(alkylthio)ethanones (**1t**, **u**, and **w**) for the OrgAKC reaction with **2a** or **2e** catalyzed by DBU, which furnished the expected 1,4,5-trisubstituted 4-thio-1,2,3-triazoles **4te**, **ue**, and **wa** in excellent yields within 0.75 h without showing any electronic effects from the alkyl substitution of sulfur (Table 4, entries 5, 6, and 8). The OrgAKC reaction of richly functionalized 1-(*p*-tolyl)-2-[(4-(trifluoromethyl)phenyl)thio]ethanone (**1v**) with 4-$CF_3C_6H_4N_3$ (**2e**) catalyzed by **3a** at 25 °C for 0.75 h furnished the functionalized 4-thio-1,2,3-triazole **4ve** in 92% yield (Table 4, entry 7). The results in Table 4 highlight the efficacy of this protocol in the click synthesis of 4-thio-1,2,3-triazoles **4**.

Table 5. Synthesis of 1,5-disubstituted 1,2,3-triazoles **5** through desulfurization of 4-thio-1,2,3-triazoles **4**.[a]



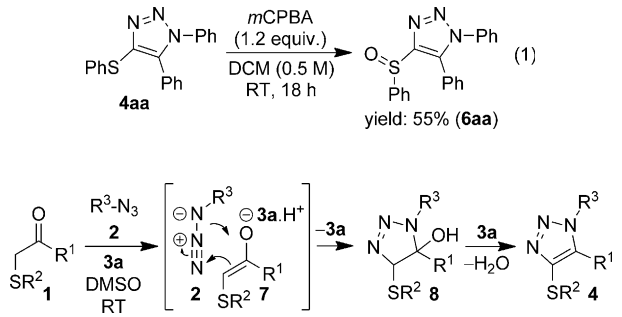
4 5

Entry	**4** (R, Ar^1, Ar^2, or Ar^3)	Yield **5** [%][b]
1	**4aa** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = C_6H_5)	87 (**5aa**)
2	**4ac** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-$CO_2EtC_6H_4$)	85 (**5ac**)
3	**4ae** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	90 (**5ae**)
4	**4ag** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-FC_6H_4)	90 (**5ag**)
5[c]	**4aj** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-BrC_6H_4)	70 (**5aa**)
6	**4ao** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = $CH_2CH_2C_6H_5$)	60 (**5ao**)
7	**4ee** (Ar^1 = 4-$CF_3C_6H_4$; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	60 (**5ee**)
8	**4le** (Ar^1 = 2-Naphthyl; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	60 (**5le**)
9	**4me** (Ar^1 = 4-PhC_6H_4; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	90 (**5me**)
10	**4re** (Ar^1 = 4-PhC_6H_4; Ar^2 = 4-ClC_6H_4; Ar^3 = 4-$CF_3C_6H_4$)	60 (**5re**)
11	**4te** (Ar^1 = 4-PhC_6H_4; R = Octyl; Ar^3 = 4-$CF_3C_6H_4$)	85 (**5te**)
12	**4ue** (Ar^1 = 4-FC_6H_4; R = Decyl; Ar^3 = 4-$CF_3C_6H_4$)	85 (**5ue**)

[a] Reactions were carried out in EtOH (0.05 M) with Raney Ni (1.0 g) and **4** (0.5 mmol) at RT; [b] yields refer to product isolated by column chromatography; [c] debromination also took place.

The advantage of the OrgAKC reaction was further depicted by synthesizing medicinally useful 1,5-disubstituted 1,2,3-triazoles **5** (Table 5). The reaction of 1,5-diphenyl-4-phenylthio-1,2,3-triazole (0.5 mmol) **4aa** with 1.0 g of freshly prepared Raney Ni in ethanol at 25 °C for 2.5 h furnished the 1,5-diphenyl-1,2,3-triazole **5aa** in 87% yield (Table 5, entry 1). This mild desulfurization reaction was further exploited by using differently substituted 4-arylthio-1,2,3-triazoles and 4-alkylthio-1,2,3-triazoles **4** (Table 5). A library of synthetically and medicinally useful 1,5-disubstituted 1,2,3-triazoles **5ac–ue** were synthesized in very good yields at room temperature by treatment of the corresponding 4-thio-1,2,3-triazoles **4** with 1.0 g of Raney Ni in ethanol through the desulfurization reaction.[18] In contrast, the reported conditions for the desulfurization required high temperature and long reaction time.[18] The desulfurization reaction worked well at 25 °C with different sulfur and aryl substituents without showing the effects of steric or electronic factors, except in the case of compound **4aj**, where debromination occurred (Table 5, entry 5). The sequential one-pot OrgAKC solvent-free reaction of **1a**, **2c**, and **3a** followed by Raney Ni desulfurization furnished the product **5ac** in reduced (65%) yield compared to the two-pot reaction (Table 5, entry 2). Pleasingly, the reaction of 1,5-diphenyl-4-phenylthio-1,2,3-triazole **4aa** with 1.2 equivalents of *m*-chloroperbenzoic acid in DCM at 25 °C for 18 h furnished selectively the monooxidized 1,5-diphenyl-4-(phenylsulfinyl)-1*H*-1,2,3-triazole **6aa** in 55% yield [Eq. (1)]. These results clearly show the advantages of the OrgAKC methodology, which enables a high-yielding synthesis of medicinally important 1,5-disubstituted 1,2,3-triazoles **5** and **6**.

A proposed mechanism for the regiospecific synthesis of **4** through the reaction of **1**, **2**, and **3a** is shown in Scheme 2. Reaction of the amine **3a** with ketone **1** generates the catalytic enolate **7**, which, on in situ treatment with Ar/R–N_3 **2**, furnishes selectively the adduct 1,2,3-triazoline **8** in a concerted



Scheme 2. Reaction mechanism for the OrgAKC.

or stepwise manner, which further converts into the 4-thio-1,2,3-triazole **4** through rapid elimination of water induced by the basic nature of amine **3 a**.

In summary, we have developed DBU-catalyzed and Raney Ni-mediated regiospecific synthesis of 1,4,5-trisubstituted 4-thio-1,2,3-triazoles **4** and 1,5-disubstituted 1,2,3-triazoles **5** from the easily available substrates 1-aryl-2-(arylthio)ethanones and 1-alkyl-2-(alkylthio)ethanones **1** with aryl or alkyl azides **2** by [3+2] cycloaddition and subsequent desulfurization, respectively. The OrgAKC reaction proceeds in very good yields with high rate and selectivity using DBU as the catalyst in 0.75 h at 25 °C; and desulfurization of **4** performed with only 1.0 g of Raney Ni at 25 °C for 1–3 h, which highlights the efficacy of this mild procedure. Further work is in progress to develop related organocatalytic enolate-mediated asymmetric click reactions.

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[1] For applications of 1,2,3-triazoles, see: a) A. C. Tome, *Sci. Synth.* **2004**, *13*, 415 – 601; b) L. S. Kallander, *J. Med. Chem.* **2005**, *48*, 5644 – 5647; c) Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674 – 1689; d) A. Tam, U. Arnold, M. B. Soellner, R. T. Raines, *J. Am. Chem. Soc.* **2007**, *129*, 12670 – 12671; e) S. Ito, A. Satoh, Y. Nagatomi, Y. Hirata, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Kawamoto, H. Ohta, *Bioorg. Med. Chem.* **2008**, *16*, 9817 – 9829; f) S. Ito, Y. Hirata, Y. Nagatomi, A. Satoh, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Ohta, H. Kawamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5310 – 5313; g) T. Tsuritani, H. Mizuno, N. Nonoyama, S. Kii, A. Akao, K. Sato, N. Yasuda, T. Mase, *Org. Process Res. Dev.* **2009**, *13*, 1407 – 1412; h) J. M. Holub, K. Kirshenbaum, *Chem. Soc. Rev.* **2010**, *39*, 1325 – 1337; i) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696 – 2718; j) see also: *Chem. Asian J.* **2011**, *6*, Issue 10 (Special Issue devoted to click chemistry); k) M. Fujinaga, T. Yamasaki, K. Kawamura, K. Kumata, A. Hatori, J. Yui, K. Yanamoto, Y. Yoshida, M. Ogawa, N. Nengaki, J. Maeda, T. Fukumura, M. R. Zhang, *Bioorg. Med. Chem.* **2011**, *19*, 102 – 110; l) I. E. Valverde, A. Bauman, C. A. Kluba, S. Vomstein, M. A. Walter, T. L. Mindt, *Angew. Chem. Int. Ed.* **2013**, *52*, 8957 – 8960; *Angew. Chem.* **2013**, *125*, 9126 – 9129; m) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A. M. Almerico, *Eur. J. Org. Chem.* **2014**, 3289 – 3306; n) S. Li, Y. Huang, *Curr. Med. Chem.* **2014**, *21*, 113 – 123.

[2] a) S. Haider, M. S. Alam, H. Hamid, *Inflamm. Cell Signal.* **2014**, *1*, doi:10.14800/ics.95; b) G. B. Silva, B. M. Guimarães, S. P. O. Assis, V. L. M. Lima, R. N. Oliveira, *J. Braz. Chem. Soc.* **2013**, *24*, 179; c) S. Shafi, *Eur. J. Med. Chem.* **2012**, *49*, 324 – 333; d) H. Miyakoshi, *J. Med. Chem.* **2012**, *55*, 6427 – 6437; e) V. S. Pore, M. A. Jagtap, S. G. Agalave, A. K. Pandey, M. I. Siddiqi, V. Kumar, P. K. Shukla, *Med. Chem. Commun.* **2012**, *3*, 484 – 488; f) Y. Morzherin, P. E. Prokhorova, D. A. Musikhin, T. V. Glukhareva, Z. Fan, *Pure Appl. Chem.* **2011**, *83*, 715 – 722.

[3] a) H. W. Bai, Z. J. Cai, S. Y. Wang, S. J. Ji, *Org. Lett.* **2015**, *17*, 2898 – 2901; b) Y. Chen, G. Nie, Q. Zhang, S. Ma, H. Li, Q. Hu, *Org. Lett.* **2015**, *17*, 1118 – 1121; c) L. Wu, Y. Chen, J. Luo, Q. Sun, M. Peng, Q. Lin, *Tetrahedron Lett.* **2014**, *55*, 3847 – 3850; d) S. Dey, T. Pathak, *RSC Adv.* **2014**, *4*, 9275 – 9278; e) A. H. Banday, V. J. Hruby, *Synlett* **2014**, *25*, 1859 – 1862; f) S. Dey, D. Datta, T. Pathak, *Synlett* **2011**, *17*, 2521 – 2524; g) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *Synthesis* **2009**, 14, 2321 – 2323; h) D. Gao, H. Zhai, M. Parvez, T. G. Back, *J. Org. Chem.* **2008**, *73*, 8057 – 8068.

[4] For CuAAC reactions, see: a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599; *Angew. Chem.* **2002**, *114*, 2708 – 2711; c) W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791 – 1815; d) *QSAR Comb. Sci.* **2007**, *26*, Issue 11 – 12 (Special Issue devoted to click chemistry); e) H. Nandivada, X. Jiang, J. Lahann, *Adv. Mater.* **2007**, *19*, 2197 – 2208; f) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333 – 2336; g) J. F. Lutz, Z. Zarafshani, *Adv. Drug Delivery Rev.* **2008**, *60*, 958 – 970.

[5] For ZnAAC, RuAAC and IrAAC reactions, see: a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998 – 15999; b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.* **2007**, *9*, 5337 – 5339; c) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923 – 8930; d) E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, *15*, 4698 – 4701; e) L. Hong, W. Lin, F. Zhang, R. Liu, X. Zhou, *Chem. Commun.* **2013**, *49*, 5589 – 5591; f) C. D. Smith, M. F. Greaney, *Org. Lett.* **2013**, *15*, 4826 – 4829.

[6] For SPAAC reactions, see: a) N. J. Agard, J. A. Preschner, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046 – 15047; b) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.* **2006**, *1*, 644 – 648; c) J. M. Baskin, C. R. Bertozzi, *QSAR Comb. Sci.* **2007**, *26*, 1211 – 1219; d) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272 – 1279; e) B. Gold, G. B. Dudley, I. V. Alabugin, *J. Am. Chem. Soc.* **2013**, *135*, 1558 – 1569.

[7] a) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4217 – 4219; b) L. Wu, Y. Chen, M. Tang, X. Song, G. Chen, X. Song, Q. Lin, *Synlett* **2012**, *23*, 1529 – 1533.

[8] a) A. Krasinski, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237 – 1240; b) D. Liu, W. Gao, Q. Dai, X. Zhang, *Org. Lett.* **2005**, *7*, 4907 – 4910; c) F. Kloss, U. Kçhn, B. O. Jahn, M. D. Hager, H. Gçrls, U. S. Schubert, *Chem. Asian J.* **2011**, *6*, 2816 – 2824.

[9] a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143 – 9147; b) M. Belkheira, D. E. Abed, J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917 – 12921; c) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584 – 3587; d) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088 – 6093; e) N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixao, *Tetrahedron* **2012**, *68*, 10456 – 10463; f) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, *19*, 13175 – 13181; g) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, *49*, 10187 – 10189; h) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.* **2013**, *15*, 2384 – 2388; i) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, *Eur. J. Org. Chem.* **2014**, 1059 – 1065; j) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.* **2014**, *16*, 3003 – 3006; k) W. Li, Z. Du, K. Zhang, J. Wang, *Green Chem.* **2015**, *17*, 781 – 784; l) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* **2015**, 3435 – 3440.

[10] a) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem. Int. Ed.* **2014**, *53*, 10420 – 10424; *Angew. Chem.* **2014**, *126*, 10588 – 10592; b) A. B. Shashank, S. Karthik, R. Madhavachary, D. B. Ramachary, *Chem. Eur. J.* **2014**, *20*, 16877 – 16881; c) W. Li, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 14186 – 14190; *Angew. Chem.* **2014**, *126*, 14410 – 14414; d) S. S. V. Ramasastry, *Angew. Chem. Int. Ed.* **2014**, *53*, 14310 – 14312;

Angew. Chem. **2014**, *126*, 14536 – 14538; e) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixão, *Chem. Commun.* **2015**, *51*, 10784 – 10796; f) J. John, J. Thomas, W. Dehaen, *Chem. Commun.* **2015**, *51*, 10797 – 10806; g) P. M. Krishna, D. B. Ramachary, P. Sruthi, *RSC Adv.* **2015**, *5*, 62062 – 62066.

[11] a) S. S. van Berkel, S. Brauch, L. Gabriel, M. Henze, S. Stark, D. Vasilev, L. A. Wessjohann, M. Abbas, B. Westermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 5343 – 5346; *Angew. Chem.* **2012**, *124*, 5437 – 5441; b) Z. Chen, Q. Yan, Z. Liu, Y. Xu, Y. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 13324 – 13328; *Angew. Chem.* **2013**, *125*, 13566 – 13570; c) Z. J. Cai, X. M. Lu, Y. Zi, C. Yang, L. J. Shen, J. Li, S. Y. Wang, S. J. Ji, *Org. Lett.* **2014**, *16*, 5108 – 5111.

[12] Z. Chen, Q. Yan, Z. Liu, Y. Zhang, *Chem. Eur. J.* **2014**, *20*, 17635 – 17639.

[13] a) J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem. Int. Ed.* **2014**, *53*, 10155 – 10159; *Angew. Chem.* **2014**, *126*, 10319 – 10323; b) A. Ali, A. G. Corrêa, D. Alves, J. Zukerman-Schpector, B. Westermann, M. A. B. Ferreira, M. W. Paixao, *Chem. Commun.* **2014**, *50*, 11926 – 11929; c) X. J. Quan, Z. H. Ren, Y. Y. Wang, Z. H. Guan, *Org. Lett.* **2014**, *16*, 5728 – 5731; d) G. Cheng, X. Zeng, J. Shen, X. Wang, X. Cui, *Angew. Chem. Int. Ed.* **2013**, *52*, 13265 – 13268; *Angew. Chem.* **2013**, *125*, 13507 – 13510; e) J. John, J. Thomas, N. Parekh, W. Dehaen, *Eur. J. Org. Chem.* **2015**, 4922 – 4930.

[14] B. T. Worrell, J. E. Hein, V. V. Fokin, *Angew. Chem. Int. Ed.* **2012**, *51*, 11791 – 11794; *Angew. Chem.* **2012**, *124*, 11961 – 11964.

[15] S. Ding, G. Jia, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 1877 – 1880; *Angew. Chem.* **2014**, *126*, 1908 – 1911.

[16] S. Horiya, J. K. Bailey, J. S. Temme, Y. V. G. Schlippe, I. J. Krauss, *J. Am. Chem. Soc.* **2014**, *136*, 5407 – 5415 and references cited therein.

[17] CCDC 1412086 (**4je**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[18] H. Hauptmann, W. F. Walter, *Chem. Rev.* **1962**, *62*, 347 – 404.

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