Facile one-pot synthesis of three different substituted thiazoles from propargylic alcohols†

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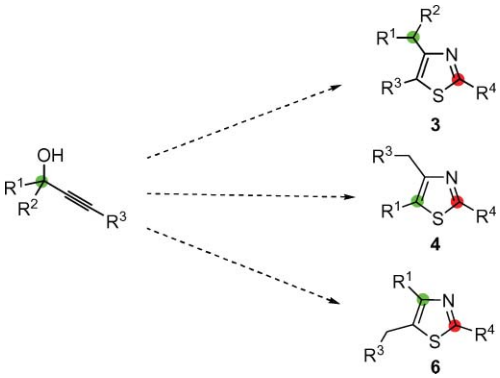
Three different substituted thiazoles have been successfully synthesized from readily available propargylic alcohols. Various secondary propargylic alcohols or tertiary propargylic alcohols participated well in the reaction, providing the desired products in good yields. This method provides a flexible and rapid route to substituted thiazoles.

Introduction

Thiazole natural products, such as the mycothiazole,[1] cystothiazole A[2] and WS75624 B,[3] are a diverse and biologically significant class of compounds in which there has been considerable interest. Because these and other natural products and pharmaceuticals containing thiazole ring, there has been intense development of methodology to construct such moieties.[4,5] Approaches toward functionalized thiazoles can be divided into two groups: functionalization of a preexisting heterocyclic core, and assembly of the ring from acyclic precursors. Among the two, the latter route has greater potential for rapidly obtaining diversity in functionalized heterocycles. Within this group, Hantzsch thiazole synthesis has proven to be a powerful method for the synthesis of thiazoles.[6] Despite the advances realized, more flexible and general routes to a variety of functionalized thiazoles are needed.[7] In particular, techniques that can readily give access to thiazoles with a diverse and easily manipulated set of substituents are still of critical importance.

We have recently reported an efficient one-pot propargylation/cycloisomerization tandem process for the synthesis of substituted oxazole derivatives from propargylic alcohols and amides employing *p*-toluenesulfonic acid monohydrate (PTSA) as a bifunctional catalyst.[8] We envisioned that replacement of the amides with thioamides would allow for the cycloaddition reaction of propargyl alcohols with thioamides to afford substituted thiazoles.[9] Herein, we describe novel methods for the synthesis of three different substituted thiazoles from propargylic alcohols (Scheme 1). A wide range of secondary propargylic alcohols or tertiary propargylic alcohols bearing not only terminal alkyne groups but also internal alkyne groups can effectively be employed, and a number of functional groups, such as cyclopropyl, cyclohexenyl, bromo, chloro, ester and methoxy, are tolerated under the reaction conditions.



Scheme 1 Synthesis of three different substituted thiazoles.

Results and discussion

Initially, propargylic alcohol **1a** and thiobenzamide **2a** were treated with 1 equiv. of PTSA in chlorobenzene at reflux. Surprisingly, this reaction didn't produce the desired product **6aa**, but 4-benzyl-2,5-diphenylthiazole **3aa**, which was obtained through an allenyl cation, and not a propargylic cation intermediate, albeit in only 12% yield (Table 1, entry 1). To further optimize the reaction shown in Table 1, we first investigated a variety of catalysts for their effectiveness at catalyzing this reaction. With other Brønsted acids, such as oxalic acid, no reaction was observed (Table 1, entry 2). We reasoned that the poor catalyst activity of Brønsted acids might be ascribed to their strong acidity. Accordingly, we began searching for appropriate Lewis acids, which would readily catalyze the cycloaddition reaction. Gratifyingly, switching the catalyst to 10 mol% AgOTf furnished the substituted thiazole **3aa** in 92% yield after 0.2 h at reflux (Table 1, entry 3). Notably, a longer reaction time is required when the catalytic amount of AgOTf decreased from 10 to 5 mol% (Table 1, entry 13 *vs.* entry 3). With $AgBF_4$ and $AgSbF_6$, the cycloaddition also proceeded smoothly to afford the thiazole **3aa** in good yields (Table 1, entries 11 and 12). $Cu(OTf)_2$ effectively promoted the cycloaddition reaction, although a somewhat long reaction time was needed (Table 1, entry 7). However, with $Sc(OTf)_3$, the cycloaddition reaction afforded the substituted thiazole in undesired yields (Table 1, entries 9 and 10).[10] In addition, it was found that the solvent played a crucial role in this cycloaddition reaction (Table 1, entries 3, 14–20). Toluene, 1,2-dichloroethane and nitromethane as solvents were

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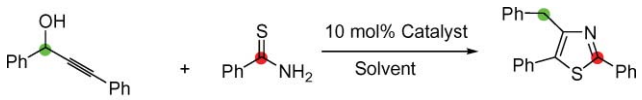
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all compounds together with copies of ^1H and ^{13}C NMR spectra of all new compounds, and X-ray data for compound **3fa**. CCDC reference number 751760. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c002093a

Table 1 Optimization of substituted thiazole formation[a]



1a 2a 3aa

Entry	Catalyst	Solvent	Time/h	Yield [%][b]
1[c]	PTSA	PhCl	1	12
2[c]	Oxalic acid	PhCl	24	0
3	AgOTf	PhCl	0.2	92
4	$BiCl_3$	PhCl	1	23
5	$InCl_3$	PhCl	1	51
6	$FeCl_3$	PhCl	12	0
7	$Cu(OTf)_2$	PhCl	1	86
8	$Zn(OTf)_2$	PhCl	1	28
9	$Sc(OTf)_3$	PhCl	1	53
10	$Sc(OTf)_3$	CH_3NO_2–H_2O (10 : 1)	1	38
11	$AgSbF_6$	PhCl	0.5	85
12	$AgBF_4$	PhCl	1	81
13[d]	AgOTf	PhCl	3	84
14	AgOTf	Toluene	4	78
15	AgOTf	CH_3CN	4	68
16	AgOTf	DCE	4	81
17	AgOTf	CH_3NO_2	1	76
18	AgOTf	DCM	24	0
19	AgOTf	THF	24	33
20	AgOTf	Acetone	24	29

[a] Reaction conditions: 10 mol% of catalyst, 1.0 equiv. of **1a** (0.5 mmol), and 1.2 equiv. of **2a** (0.6 mmol) in solvent (2 mL) at reflux. [b] Isolated yield of pure product based on propargylic alcohol **1a**. [c] 1.0 equiv. [d] 5 mol% AgOTf.

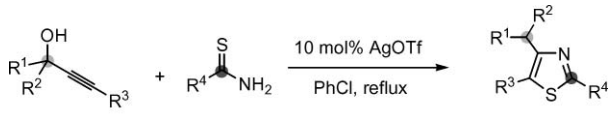
also able to facilitate the cycloaddition reaction. However, the use of chlorobenzene instead of toluene, 1,2-dichloroethane and nitromethane obviously reduced the reaction time (Table 1, entry 3 *vs.* entries 14, 16 and 17). The results of solvents screened showed that the reaction rates were influenced by various factors, such as boiling point, polarity, *etc.* Because the cycloaddition reaction proceeded under reflux, the boiling point of solvents might be a main factor. However, the detailed mechanism is still not clear.

With these optimal reaction conditions in hand, we examined the scope of this cycloaddition reaction. Typical results are shown in Table 2. To our delight, all the secondary propargylic alcohols and tertiary propargylic alcohols **1** bearing not only terminal alkyne groups but also internal alkyne groups participated well in the cycloaddition reaction, producing the cycloaddition products in good yields. The reaction is completed rapidly under mild conditions and is tolerant to air, giving water as the only byproduct. It should also be noted that groups such as cyclopropyl, cyclohexenyl, bromo, ester, and methoxy in the propargylic alcohols were readily carried through the cycloaddition reaction, allowing for the subsequent elaboration of the products.

Secondary propargylic alcohol **1h** possessing an electron-donating group at the aryl ring reacted smoothly with thioamide **2a** affording the thiazole **3ha** in 94% yield (Table 2, entry 8). Moreover, substrates **1i** and **1j** possessing electron-withdrawing groups (bromo and ester functionalities) at the aryl ring were also successfully employed in the cycloaddition reaction to give the thiazoles **3ia** and **3ja** in 85 and 74% yields with complete regioselectivity, respectively (Table 2, entries 9 and 10). Obviously, electron-rich propargylic alcohols provided the desired products in higher yields than electron-poor propargylic alcohols. Secondary propargylic alcohols possessing a straight chain saturated alkyl on the alkyne part (R^3 = *n*-Bu) reacted rapidly with a series of thioamides, providing the corresponding cycloaddition products in high yields with complete regioselectivity (Table 2, entries 2, 5, 7–9, 16 and 18–21). Remarkably, the expected cyclopropyl thiazoles (R^3 = cyclopropyl) were obtained readily, and no ring-opening of the cyclopropyl groups was observed (Table 2, entries 3 and 24). When R_3 is an olefin, the cycloaddition also led to the formation of the thiazoles (R^3 = cyclohexenyl) in good yields (Table 2, entries 4 and 25). Additionally, heteroaromatic propargylic alcohol **1e** and fused aromatic propargylic alcohol **1g** readily underwent cycloaddition reaction to afford the substituted thiazoles **3ea** and **3ga** in desired yields with complete regioselectivity, respectively (Table 2, entries 5 and 7). Most notably, secondary propargylic alcohol **1f** containing a substituted olefin that is susceptible to protonation also reacted smoothly with thioamide to give **3fa** in 71% yield with complete regioselectivity (Table 2, entry 6). The crystallization of compound **3fa** from ethanol gave single crystals suitable for X-ray analysis. Fig. 1 illustrates the molecular structure of the substituted thiazole **3fa**.[11] The X-ray structure of **3fa** shows the expected five-membered (C11–S1–C12–N1–C10) aromatic ring skeleton. Thiazole **3fa** adopts a *trans*-configuration, in which the two hydrogen atoms are on opposite side of the double bond (C7=C8). The X-ray crystal structure also reveals that the dihedral angle between plane 1 (defined by atoms C13–C18) and plane 2 (S1, N1 and C10–C12) is 18.66 (0.28)°, and the dihedral angle between plane 2 (S1, N1 and C10–C12) and plane 3 (C19–C24) is 47.04 (0.2)°.

Tertiary propargylic alcohols could also participate in the cycloaddition with thioamide using silver triflate as a catalyst

Table 2 Synthesis of substituted thiazoles **3aa–3dh** from propargylic alcohols **1a–1o** and thioamides **2a–2h**[a]



1a-1o **2a-2h** **3aa-3dh**

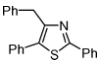
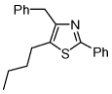
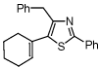
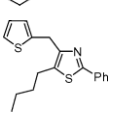
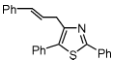
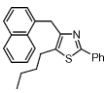
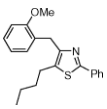
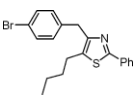
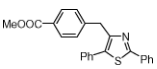
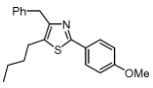
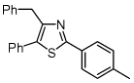
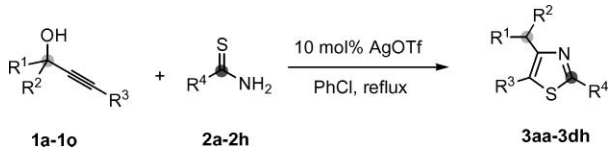
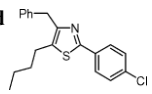
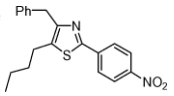
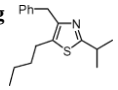
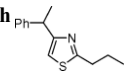
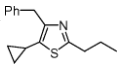
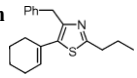
Entry	R^1; R^2; R^3	R^4	Product	Time/h	Yield [%][b]
1	**1a**: Ph; H; Ph	**2a**: Ph	**3aa** 	0.2	92
2	**1b**: Ph; H; *n*-Bu	**2a**: Ph	**3ba** 	0.5	87
3	**1c**: Ph; H; cyclopropyl	**2a**: Ph	**3ca** 	0.3	89
4	**1d**: Ph; H; 1-cyclohexenyl	**2a**: Ph	**3da** 	0.3	90
5	**1e**: 2-Thienyl; H; *n*-Bu	**2a**: Ph	**3ea** 	0.5	88
6	**1f**: (*trans*)PhCH=CH; H; Ph	**2a**: Ph	**3fa** 	0.4	71
7	**1g**: 1-Naphthyl; H; *n*-Bu	**2a**: Ph	**3ga** 	0.4	88
8	**1h**: 2-MeOPh; H; *n*-Bu	**2a**: Ph	**3ha** 	0.2	94
9	**1i**: 4-BrPh; H; *n*-Bu	**2a**: Ph	**3ia** 	0.5	85
10	**1j**: 4-MeOOCPh; H; Ph	**2a**: Ph	**3ja** 	1	74
11	**1k**: Ph; Ph; Ph	**2a**: Ph	**3ka** 	0.2	95
12	**1l**: Ph; Me; TMS	**2a**: Ph	**3la** 	0.2	89
13	**1m**: Ph; Me; H	**2a**: Ph	**3la** 	0.3	83
14[c]	**1n**: Me; Me; Ph	**2a**: Ph	**3na** 	24	58
15[c]	**1o**: -$(CH_2)_5$-; Ph	**2a**: Ph	**3oa** 	24	42
16	**1b**: Ph; H; *n*-Bu	**2b**: 4-MeOPh	**3bb** 	0.5	89
17	**1a**: Ph; H; Ph	**2c**: 4-CH_3Ph	**3ac** 	0.2	91

Table 2 *(Contd.)*



1a-1o 2a-2h 3aa-3dh

Entry	R^1; R^2; R^3	R^4	Product	Time/h	Yield [%][b]
18	**1b**: Ph; H; *n*-Bu	**2d**: 4-ClPh	**3bd** 	0.8	84
19	**1b**: Ph; H; *n*-Bu	**2e**: 4-NO_2Ph	**3be** 	1	68
20	**1b**: Ph; H; *n*-Bu	**2f**: Me	**3bf** 	1	77
21	**1b**: Ph; H; *n*-Bu	**2g**: *i*-Pr	**3bg** 	1	82
22	**1a**: Ph; H; Ph	**2f**: Me	**3af** 	1	80
23	**1m**: Ph; Me; H	**2h**: *n*-Pr	**3mh** 	1	79
24	**1c**: Ph; H; cyclopropyl	**2h**: *n*-Pr	**3ch** 	1	83
25	**1d**: Ph; H; 1-cyclohexenyl	**2h**: *n*-Pr	**3dh** 	1	86

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), and AgOTf (0.05 mmol) in chlorobenzene (2 mL) at reflux. See the ESI for details.† [b] Isolated yield of pure product based on propargylic alcohols **1**. [c] The solvent is nitromethane.

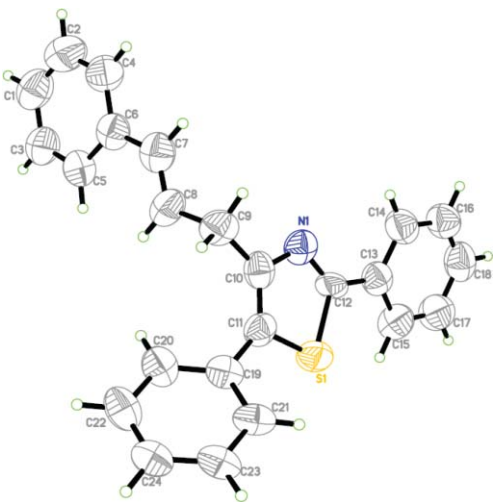


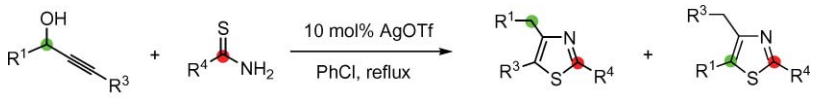
Fig. 1 X-ray crystal structure of thiazole **3fa**. The thermal ellipsoids are at the 50% probability level.

(Table 2, entries 11–15). 10 mol% AgOTf catalyzed the selective cycloaddition of tertiary aromatic propargylic alcohols **1k–1m** and thioamide, affording **3** in high yields (Table 2, entries 11–13). The tertiary aliphatic propargylic alcohols **1n** and **1o** also reacted with thioamide affording thiazoles **3na** and **3oa** in moderate yields with complete regioselectivity (Table 2, entries 14 and 15). This is in sharp contrast to the Sc-catalyzed reaction[7] where the substrates are limited to the secondary aromatic propargylic alcohols (R^1 = aryl, R^2 = H, R^3 = SPh or SePh). The results suggested that the cycloaddition proceeded through a cationic intermediate and the yield of the cycloaddition reaction was dependent on the stability of the cationic intermediate. Instability of the cationic intermediate of the tertiary aliphatic propargylic alcohols made the cycloaddition reaction less favorable.

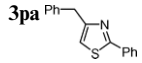
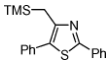
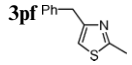
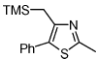
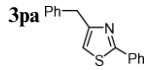
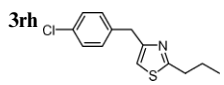
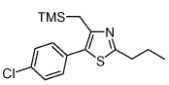
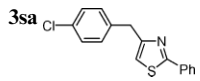
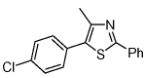
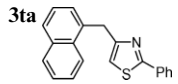
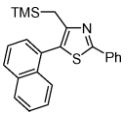
A variety of thioamides **2** were also employed to examine the generality of the method. Both aromatic thioamides and aliphatic thioamides could be efficiently incorporated into the thiazole framework. The cycloaddition reaction proceeded smoothly when the aryl groups of the aromatic thioamides were substituted with electron-donating (Table 2, entry 16) and electron-withdrawing groups (Table 2, entry 19). Electron-rich groups are beneficial to the cycloaddition reaction. Aliphatic thioamides required slightly longer reaction times, but maintained high yields (Table 2, entries 20–25).

Interestingly, Table 3 shows that the attempted cycloaddition of secondary propargylic alcohols **1p–1t** (R^3 = TMS or H)

Table 3 Synthesis of substituted thiazoles **3pa–3ta** and **4pa–4ta** from propargylic alcohols **1p–1t** and thioamides **2**[a]



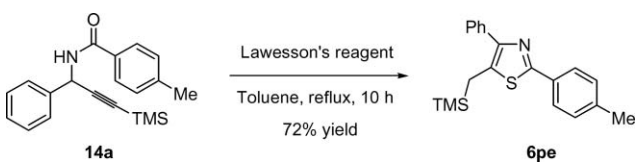
1p-1t 2 3pa-3ta 4pa-4ta

Entry	Propargylic alcohol	Thioamide	Product 3	Product 4	Time/h	Yield [%][b] (ratio **3**:**4**)[c]
1	**1p**: R^1 = Ph; R^3 = TMS	**2a**: R^4 = Ph	**3pa** 	**4pa** 	1	87 (29 : 71)
2	**1p**: R^1 = Ph; R^3 = TMS	**2f**: R^4 = Me	**3pf** 	**4pf** 	2	83 (24 : 76)
3	**1q**: R^1 = Ph; R^3 = H	**2a**: R^4 = Ph	**3pa** 	**4qa** 	1.5	76 (8 : 92)
4	**1r**: R^1 = 4-ClPh; R^3 = TMS	**2h**: R^4 = *n*-Pr	**3rh** 	**4rh** 	2	79 (21 : 79)
5	**1s**: R^1 = 4-ClPh; R^3 = H	**2a**: R^4 = Ph	**3sa** 	**4sa** 	2	72 (7 : 93)
6	**1t**: R^1 = 1-Naphthyl; R^3 = TMS	**2a**: R^4 = Ph	**3ta** 	**4ta** 	1	89 (75 : 25)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), and AgOTf (0.05 mmol) in chlorobenzene (2 mL) at reflux. See the ESI for details.† [b] Isolated yield of pure product based on propargylic alcohols **1**. [c] Determined by ^{1}H NMR.

with thioamides led to the formation of the substituted thiazoles **4** as the major products, and the substituted thiazoles **3** were observed as only the minor products. Remarkably, the structure of the substituted thiazoles **4** differed from that of the substituted thiazoles **3**. Typical results are depicted in Table 3. Secondary propargylic alcohols (R^3 = TMS) reacted smoothly with thioamides **2** affording the substituted thiazoles **3** and **4** in high yields with moderate selectivity (**3**:**4** = 21 : 79–75 : 25) (Table 3, entries 1, 2, 4 and 6). The trimethylsilyl group attached to the thiazole ring could not be tolerated under the acidic conditions and had fallen off during work-up. Notably, with the use of secondary terminal propargylic alcohols (R^3 = H) as substrates, the regioselectivity of the cycloaddition reaction was greatly improved. For example, secondary terminal propargylic alcohol **1q** (R^3 = H) readily underwent cycloaddition to give the substituted thiazoles **3pa** and **4qa** in total yield of 76% with high selectivity (**3pa** : **4qa** = 8 : 92) (Table 3, entry 3). The cycloaddition reaction of propargylic alcohols bearing terminal alkyne (R^3 = H) with thioamides showed high regioselectivity toward the substituted thiazoles **4**, and provided a rapid route to the substituted thiazoles **4**.

As results of the development on the transition metal-catalyzed nucleophilic substitution of propargylic alcohols in our group,[12] we wish to report a highly efficient propargylation/sulfuration/cyclization reaction for the synthesis of substituted thiazoles directly from propargylic alcohols, amide and Lawesson's Reagent (2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide), as shown in Table 4. Initially, propargylic alcohol **1a** (0.5 mmol) was treated with amide **5a** (0.55 mmol) in the presence of 10 mol% $FeCl_3$ in acetonitrile. Upon reaction completion, acetonitrile was removed *in vacuo*, followed by the addition of toluene (2 mL) and Lawesson's reagent (0.55 mmol). The reaction was heated to reflux for 10 h. The desired product **6aa** was obtained in 50% yield. Typical results are depicted in Table 4. Various secondary aromatic propargylic alcohols participated well in the reaction, providing the propargylation/sulfuration/cyclization products with complete regioselectivity. Both aromatic amides (Table 4, entries 1–3 and 5–8) and aliphatic amides (Table 4, entry 4) could be efficiently incorporated into the thiazole framework. It should be noted that the structure of the substituted thiazoles **6** differed completely from that of the substituted thiazoles **3** and **4**. Formation of product **6pe** was also observed by treating compound **14a** with Lawesson's reagent in the absence of 10 mol% $FeCl_3$ (Scheme 2). This result clearly showed that $FeCl_3$ was not essential in the cyclization step of the sequential reactions.

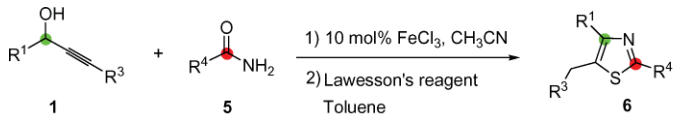


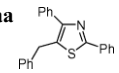
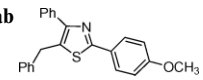
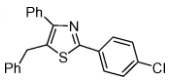
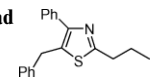
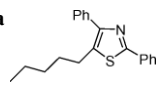
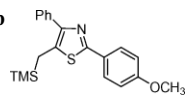
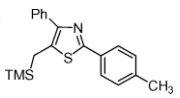
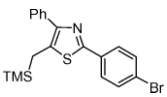
14a 6pe

Scheme 2 Reactions of alkynyl-amide **14a** with Lawesson's reagent.

On the basis of these data, we propose the process detailed in Scheme 3 as the most likely mechanism for this transformation.

Table 4 Synthesis of substituted thiazoles **6** from propargylic alcohols **1** and amides **5**[a]



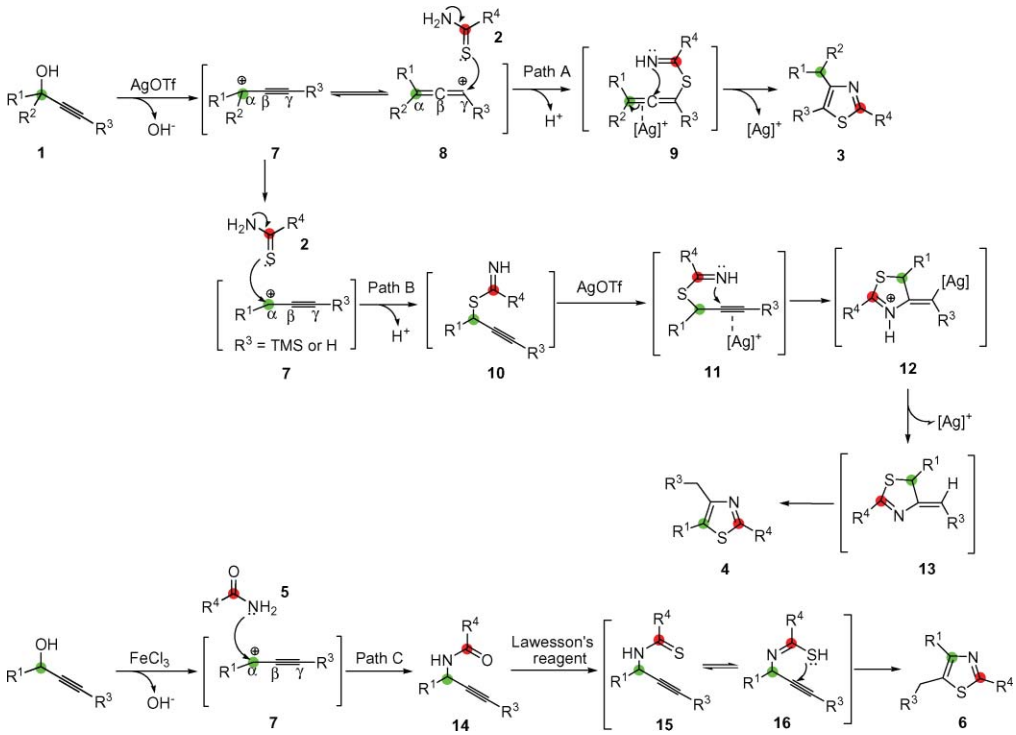
Entry	R^1; R^3	R^4	Product	Time/h[b]	Yield [%][c]
1	**1a**: Ph; Ph	**5a**: Ph	**6aa** 	17	50
2	**1a**: Ph; Ph	**5b**: 4-MeOPh	**6ab** 	17	53
3	**1a**: Ph; Ph	**5c**: 4-ClPh	**6ac** 	17	47
4	**1a**: Ph; Ph	**5d**: *n*-Pr	**6ad** 	17	41
5	**1b**: Ph; *n*-Bu	**5a**: Ph	**6ba** 	17	46
6	**1p**: Ph; TMS	**5b**: 4-MeOPh	**6pb** 	20	51
7	**1p**: Ph; TMS	**5e**: 4-CH_3Ph	**6pe** 	20	50
8	**1p**: Ph; TMS	**5f**: 4-BrPh	**6pf** 	20	47

[a] Reaction conditions: **1** (0.5 mmol), **5** (0.55 mmol), and $FeCl_3$ (0.05 mmol) in CH_3CN (2 mL) at 70 °C for 7 h, or at 80 °C for 10 h (for substrate **1p**). Upon reaction completion, acetonitrile was removed *in vacuo*, followed by the addition of toluene (2 mL) and Lawesson's reagent (0.6 mmol). Cycloisomerization proceeded at reflux for 10 h. [b] Overall teaction time for three steps. [c] Isolated yield of pure product based on propargylic alcohols **1**.

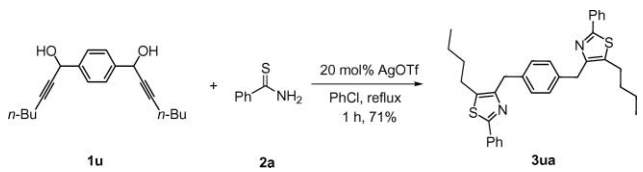
For the silver-catalyzed cycloaddition reaction of propargylic alcohols with thioamides, the propargylic cation **7** or the allenyl cation **8** is attacked firstly by the sulfur atom of the thioamides. The secondary propargylic alcohols (R^3 = alkyl or aryl) or tertiary propargylic alcohols follow path A. In path A, the ionization of propargylic alcohol **1** would firstly lead to propargylic cation **7**. The propargyl cation would isomerize to the allenyl cation **8** and the subsequent nucleophilic attack of the thioamide **2** gives intermediate **9**, which easily cyclizes in the *5-exo-dig* mode, leading to the thiazole **3**. At the same time, the secondary propargylic alcohols (R^3 = TMS or H) follow both path A and path B, but cycloaddition proceeds mainly *via* path B. When the secondary propargylic alcohols (R^3 = TMS or H) are used, instability of the allenyl cation intermediate **8** (R^3 = H) and the steric effect of trimethylsilane group at γ-position of the intermediate **8** (R^3 = TMS) makes path A less favorable. Accordingly, the cycloaddition would also proceed through path B, which is more favorable. In path B, the reaction of the propargylic cation **7** and the thioamide **2** gives intermediate **10**. Coordination of cationic silver(I) to the alkyne forms the π-alkyne silver complex **11** and enhances the electrophilicity of the alkyne. Subsequent *5-exo-dig* nucleophilic attack of the amido group would generate the alkenyl-silver derivative **12**. Protonolysis of **12** affords dihydrothiazole **13**, which then undergoes isomerization to the thiazole **4**.

Nevertheless, secondary propargylic alcohol **1t** (R^1 = naphthyl, R^3 = TMS) reacted rapidly with thiobenzamide to produce the thiazole **3ta** as a major product (Table 2, entry 6), possibly due to the steric bulkiness of the naphthyl group at the α-position of the intermediate **7**. On the other hand, for the propargylation/sulfuration/cyclization reaction of propargylic alcohols, amide and Lawesson's Reagent, the propargylic cation **7** is attacked firstly by the nitrogen atom of the amides. In path C, propargylic cation **7** underwent nucleophilic attack of the amide **5**, giving alkynyl-amide **14**, which was easily converted to alkynyl-thioamide **15** in the present of Lawesson's Reagent. The subsequent cycloisomerization of **15** gives the final product **6**.

In addition, the silver-catalyzed cycloaddition reaction also proceeded well with symmetrical propargylic alcohols, allowing for the synthesis of oligomers containing two thiazole moieties. For example, symmetrical propargylic alcohol **1u** underwent silver-catalyzed cycloaddition reaction to afford the oligomer **3ua** in 71% isolated yield with complete regioselectivity (Scheme 4). This process has the potential to access oligoaryls that show promise as new optoelectronic materials.[13]



Scheme 3 Proposed mechanism for the synthesis of three different substituted thiazoles.



Scheme 4 Synthesis of the oligomer **3ua**.

Conclusions

In summary, three different substituted thiazoles have been successfully synthesized from readily available propargylic alcohols. The reaction is proposed to proceed through an allenyl isomer or propargylic cation intermediate. The readily available substrates, broad scope and operational simplicity of this process should be beneficial for its large-scale application. Study on the development of the cycloaddition reaction is ongoing in our laboratory.

Experimental

General experimental

Propargylic alcohols **1** and thiobenzamides **2** were prepared according to published procedures. All other compounds are commercially available and were used without further purification. Infrared spectra were recorded on a Nicolet AVATER FTIR360 spectrometer. NMR spectra were recorded on a Bruker AVANCE DPX-400 instrument at 400 MHz (^{1}H) or 100 MHz (^{13}C). The chemical shift values (δ) are given in parts per million (ppm) and are referred to the residual peak of the deuterated solvent ($CDCl_3$). MS measurements were performed on Bruker Reflex III mass spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 microanalyser. Flash chromatography was performed with QingDao silica gel (300–400 mesh).

General procedure for the synthesis of substituted thiazoles 3 and 4. To a 5 mL flask, propargylic alcohols[14] **1** (0.5 mmol), thioamides[15] **2** (0.6 mmol), chlorobenzene (2.0 mL) and AgOTf (0.05 mmol) were successively added. The reaction mixture was stirred at reflux, and monitored periodically by TLC. Upon completion, the chlorobenzene was removed under reduced pressure, and then the residue was purified by silica gel column chromatography (EtOAc–hexane) to afford the corresponding substituted thiazoles **3** (or two regioisomers **3** and **4**).

General procedure for the synthesis of substituted thiazoles 6. To a 5 mL flask, propargylic alcohols **1** (0.5 mmol), amides **5** (0.55 mmol), acetonitrile (2.0 mL) and $FeCl_3$ (0.05 mmol) were successively added. The reaction was allowed to stir at 70–80 °C, and monitored periodically by TLC. Upon reaction completion, acetonitrile was removed *in vacuo*, followed by the addition of toluene (2 mL) and Lawesson's reagent (0.55 mmol). The reaction mixture was heated to reflux temperature for an additional 10 h until completion. Upon completion, the toluene was removed under reduced pressure, and then the residue was purified by silica gel column chromatography (EtOAc–hexane) to afford the corresponding substituted thiazoles **6**.

Acknowledgements

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Notes and References

1 (*a*) P. Crews, Y. Kakou and E. Quinoa, *J. Am. Chem. Soc.*, 1988, **110**, 4365; (*b*) A. Cutignano, I. Bruno, G. Bifulco, A. Casapullo, C. Debitus, L. Gomez-Paloma and R. Riccio, *Eur. J. Org. Chem.*, 2001, 775.

2 (*a*) D. R. Williams, S. Patnaik and M. P. Clark, *J. Org. Chem.*, 2001, **66**, 8463; (*b*) P. L. DeRoy and A. B. Charette, *Org. Lett.*, 2003, **5**, 4163.

3 (*a*) S. Yoshimura, Y. Tsuruni, S. Takase and M. Okuhara, *J. Antibiot.*, 1995, **48**, 1073; (*b*) Y. Tsuruni, H. Ueda, K. Hayashi, S. Takase, M. Nishikawa, S. Kiyoto and M. Okuhara, *J. Antibiot.*, 1995, **48**, 1066.

4 For a few selected reviews, see: (*a*) J. V. Metzger, *Comprehensive Heterocyclic Chemistry*, ed. R. Katrizky and C. W. Rees, Pergamon, New York, 1984, Vol. 6, p 235; (*b*) P. Wipf, *Chem. Rev.*, 1995, **95**, 2115; (*c*) T. S. Jagodziński, *Chem. Rev.*, 2003, **103**, 197; (*d*) S. M. Mustafa, V. A. Nair, J. P. Chittoor and S. Krishnapillai, *Mini-Rev. Org. Chem.*, 2004, **1**, 375; (*e*) Y. -J. Wu and B. V. Yang, Five-membered ring systems: with N and S (Se, Te) atoms, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and J. A. Joule, Elsevier, Oxford, 2007, Vol. 18, p 247; (*f*) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 382.

5 For a few selected examples, see: (*a*) P. Wipf and S. Venkatraman, *J. Org. Chem.*, 1996, **61**, 8004; (*b*) C. P. Ball, A. G. M. Barrett, D. Compère, C. Kuhn, R. S. Roberts, M. L. Smith, O. Venier and A. Commerçon, *Chem. Commun.*, 1998, 2019; (*c*) P. Wipf, L. T. Rahman and S. R. Rector, *J. Org. Chem.*, 1998, **63**, 7132; (*d*) I. Y. Lee, J. Y. Lee, H. J. Lee and Y.-D. Gong, *Synlett*, 2005, 2483; (*e*) U. Kazmaier and S. Ackermann, *Org. Biomol. Chem.*, 2005, **3**, 3184; (*f*) M. Narender, M. S. Reddy, R. Sridhar, Y. V. D. Nageswar and K. R. Rao, *Tetrahedron Lett.*, 2005, **46**, 5953; (*g*) M. Umkehrer, J. Kolb, C. Burdack and W. Hiller, *Synlett*, 2005, 79; (*h*) Z. Kaleta, B. T. Makowski, T. Soós and R. Dembinski, *Org. Lett.*, 2006, **8**, 1625; (*i*) T. M. Potewar, S. A. Ingale and K. V. Srinivasan, *Tetrahedron*, 2007, **63**, 11066; (*j*) D. Thomae, E. Perspicace, Z. Xu, D. Henryon, S. Schneider, S. Hesse, G. Kirsch and P. Seck, *Tetrahedron*, 2009, **65**, 2982; (*k*) B. Shi, A. J. Blake, W. Lewis, I. B. Campbell, B. D. Judkins and C. J. Moody, *J. Org. Chem.*, 2010, **75**, 152.

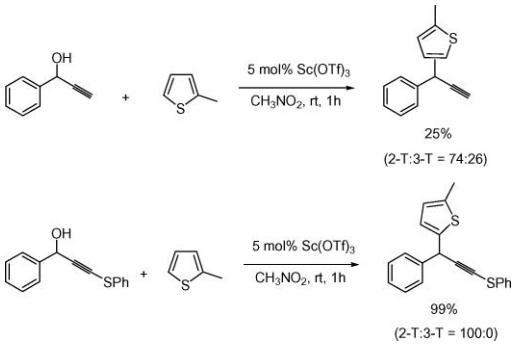
6 T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, Wiley-VCH, Weinheim, 2nd edn, 2003.

7 During the preparation ofthis manuscript, a $Sc(OTf)_3$-catalyzed cycloaddition reaction of 3-sulfanylpropargyl alcohols or 3-selanylpropargyl alcohols with thioamides was reported. However, the substrates of this method are limited to the secondary aromatic 3-sulfanylpropargyl alcohols or secondary aromatic 3-selanylpropargyl alcohols. See: M. Yoshimatsu, T. Yamamoto, A. Sawa, T. Kato, G. Tanabe and O. Muraoka, *Org. Lett.*, 2009, **11**, 2952.

8 Y.-M. Pan, F.-J. Zheng, H.-X. Lin and Z.-P. Zhan, *J. Org. Chem.*, 2009, **74**, 3148.

9 Recently, the Nishibayashi team has tried to obtain the thiazoles by the reaction of propargylic alcohols with thiobenzamide in the presence of ruthenium and gold catalysts, but it was unsuccessful. See: M. D. Milton, Y. Inada, Y. Nishibayashi and S. Uemura, *Chem. Commun.*, 2004, 2712.

10 In the $Sc(OTf)_3$-catalyzed propargylations and cycloaddition of 3-sulfanylpropargyl alcohols or 3-selanylpropargyl alcohols, γ-sulfanyl or γ-selanyl functional groups play an important role. Either the sulfur or the selenium atom stabilizes the propargyl cation and the allenyl cation, and promotes the propargylations and cycloaddition, *e.g.* See:



(*a*) M. Yoshimatsu, T. Otani, S. Matsuda, T. Yamamoto and A. Sawa, *Org. Lett.*, 2008, **10**, 4251; (*b*) ref. 7.

11 Crystal data for **3fa**: $C_{24}H_{19}NS$, $M = 353.46$, orthorhombic, space group *Fdd2*, $a = 17.699(4)$ Å, $b = 74.502(18)$ Å, $c = 5.7208(14)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 7544(3)$ Å^3, $Z = 16$, $Dc = 1.245$ Mg m^{-3}, $\mu = 0.178$ mm^{-1}, 14565 reflections, 3678 unique ($R_{int} = 0.1042$), $R[F^2 > 2\sigma(F^2)] = 0.0722$, w$R(F^2) = 0.2081$, Flack value = 0.02(18). CCDC 751760.

12 We have reported that the $FeCl_3$-catalyzed nucleophilic substitution of propargylic alcohols with amides in acetonitrile affords the alkynylamides in good yields. See: Z.-P. Zhan, J.-L. Yu, H.-J. Liu, Y.-Y. Cui, R.-F. Yang, W.-Z. Yang and J.-P. Li, *J. Org. Chem.*, 2006, **71**, 8298.

13 (*a*) C.-F. Lee, L.-M. Yang, T.-Y. Hwu, A.-S. Feng, J.-C. Tseng and T.-Y. Luh, *J. Am. Chem. Soc.*, 2000, **122**, 4992; (*b*) J. F. Hulvat, M. Sofos, K. Tajima and S. I. Stupp, *J. Am. Chem. Soc.*, 2005, **127**, 366; (*c*) M. Sato and A. Yoshizawa, *Adv. Mater.*, 2007, **19**, 4145.

14 The propargyl alcohols were prepared from aldehyde or ketone and alkyne. See: M. Egi, Y. Yamaguchi, N. Fujiwara and S. Akai, *Org. Lett.*, 2008, **10**, 1867.

15 The thioamides were prepared from amides and Lawesson's reagent. See: S. J. Coats, J. S. Link and D. J. Hlasta, *Org. Lett.*, 2003, **5**, 721.

