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Facile Synthesis of 2,5-Disubstituted Thiazoles from Terminal Alkynes, Sulfonyl Azides, and Thionoesters

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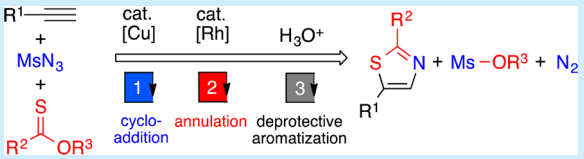
Supporting Information

ABSTRACT: A sequential procedure for the synthesis of 2,5-disubstituted thiazoles from terminal alkynes, sulfonyl azides, and thionoesters is reported. A copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes with sulfonyl azides affords 1-sulfonyl-1,2,3-triazoles, which then react with thionoesters in the presence of a rhodium(II) catalyst. The resulting 3-sulfonyl-4-thiazolines subsequently aromatize into the corresponding 2,5-disubstituted thiazoles by elimination of the sulfonyl group.



A thiazole ring represents a privileged structural motif often found in natural products and pharmaceutically active substances.[1] Moreover, thiazoles multisubstituted with aryl groups are core components constituting materials of interesting optical[2] and electronic properties.[3] The condensation reaction of α-halocarbonyl compounds with thioamides, named Hantzsch thiazole synthesis, is the most widely used and reliable procedure for their preparation.[4] However, 2,5-disubstituted thiazoles are less accessible with the Hantzsch thiazole synthesis[5] because chemically labile α-haloaldehydes are required for their synthesis. An alternative method to synthesize those substituted thiazoles is given by palladium-catalyzed C−H arylation reactions of thiazoles with aryl halides, in which an aryl substituent is installed onto a preformed thiazole core.[6] On the other hand, the synthetic methods to directly construct thiazole skeletons possessing 2,5-disubstituents from easily available simple starting substances are still limited.[7,8] We now report a facile method to synthesize 2,5-disubstituted thiazoles from terminal alkynes, sulfonyl azides, and thionoesters (Figure 1). The transformation

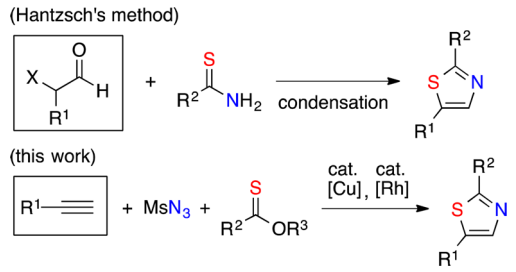
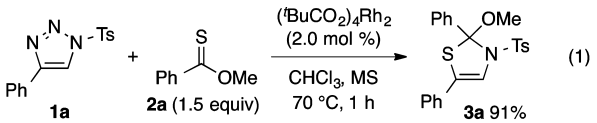
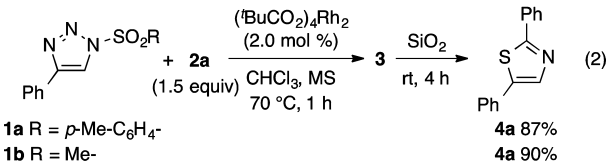


Figure 1. Construction of 2,5-disubstituted thiazoles.

consists of two catalytic reactions; a copper(I)-catalyzed 1,3-diploar cycloaddition of terminal alkynes with sulfonyl azides[9] and a rhodium(II)-catalyzed reaction of the resulting 1-sulfonyl-1,2,3-triazoles with thionoesters.

Recently, 1-sulfonyl-1,2,3-triazoles have received much attention as the precursors of α-imino metal carbene complexes.[10] The generated carbene complex possesses an electrophilic carbene carbon and a nucleophilic imino nitrogen in the molecule. They act as the 1,3-dipoles in a formal sense in the reactions with a variety of dipolarophiles, which include alkynes,[11] allenes,[12] nitriles,[13] aldehydes and imines,[14] isocyanates and isothiocyanates,[15] and indoles,[16] affording the corresponding [3 + 2] cycloadducts. In the present study, we examined if thionoesters could serve as the suitable dipolarophiles.[17] First, we prepared *O*-methyl benzothioate (**2a**) from methyl benzoate and the Lawesson's reagent according to a literature procedure.[18] Then, 4-phenyl-1-tosyl-1,2,3-triazole (**1a**, 1.0 equiv) was treated with **2a** (1.5 equiv) in the presence of $(^t\mathrm{BuCO_2})_4\mathrm{Rh_2}$ (2.0 mol %) and 4 Å molecular sieves (MS)[19] in chloroform (2 mL) at 70 °C (eq 1). The triazole **1a** was





consumed in 1 h, and after chromatographic purification using modified silica gel, 2,5-diphenyl-2-methoxy-3-tosyl-4-thiazoline (**3a**) was obtained in 91% isolated yield. The structure of **3a** was confirmed by its single-crystal X-ray analysis. The thiazoline **3a** was labile under acidic conditions to readily aromatize by elimination of a sulfonyl group. Thus, when acidic silica gel was directly added to the reaction mixture containing **3a**, elimination of methyl 4-methylbenzenesulfonate occurred to afford 2,5-diphenylthiazole (**4a**) in 87% yield based on **1a** (eq 2). 1-Mesyl-

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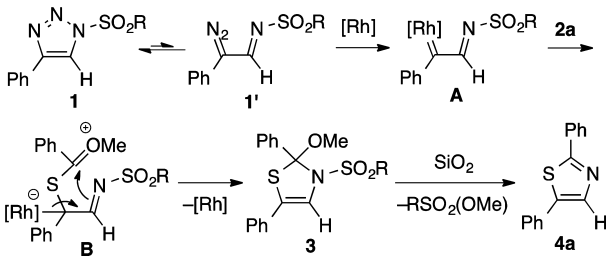
substituted triazole **1b** also reacted well with **2a** to give a slightly better yield of **4a** (90%).

A plausible mechanism for the production of the thiazole **4a** from 1-sulfonyl-1,2,3-triazole **1** and *O*-methyl benzothioate (**2a**) is depicted in Scheme 1. Initially, a reversible ring−chain

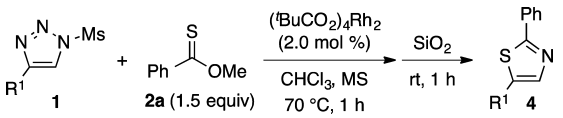
Scheme 1. Proposed Mechanism for the Formation of Thiazole 4a



tautomerization of **1** generates *α*-diazoimine **1′**, which reacts with rhodium(II) to afford *α*-imino rhodium carbene complex **A** with extrusion of molecular nitrogen. The sulfur of **2a** attacks the electrophilic carbene center of **A** to furnish zwitterionic intermediate **B**.[20] The anionic rhodium releases an electron pair, which induces the addition of the imino nitrogen to the carbon of the oxonium ion, forming a five-membered ring. The resulting 4-thiazoline **3** readily aromatizes upon treatment with acidic silica gel by elimination of methyl sulfonate to give the thiazole **4a**.

A variety of triazoles **1** were subjected to the sequential reaction with *O*-methyl benzothioate (**2a**) (Table 1). Triazoles

Table 1. Rh(II)-Catalyzed Reaction of Various Triazoles 1 with 2a[a]



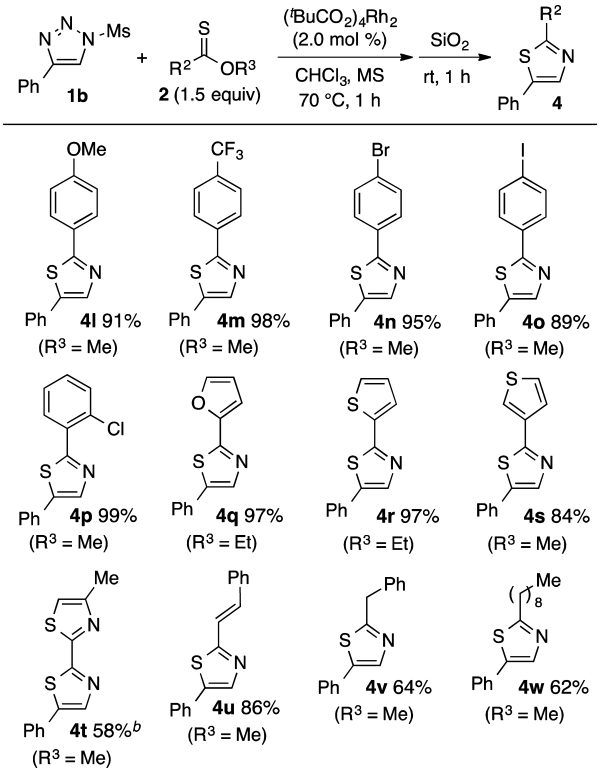
entry	triazole **1**		product **4**	yield (%)[b]
	R^1			
1	*p*-Me-C_6H_4-	**1c**	**4b**	96
2	*p*-MeO-C_6H_4-	**1d**	**4c**	84
3	*p*-CF_3-C_6H_4-	**1e**	**4d**	90
4	*p*-Br-C_6H_4-	**1f**	**4e**	96
5	*o*-Br-C_6H_4-	**1g**	**4f**	91
6	*p*-I-C_6H_4-	**1h**	**4g**	87
7	*p*-(pin)B-C_6H_4-	**1i**	**4h**	67
8	3-Thienyl-	**1j**	**4i**	98
9	1-Cyclohexenyl-	**1k**	**4j**	87
10	*n*-Propyl-	**1l**	**4k**	49[c]

[a]On a 0.20 mmol scale. [b]Isolated yield. [c]Ts-substituted triazole **1l** and **2a** (5.0 equiv) were used.

1c−i, possessing an aryl group at the 4-position, afforded the corresponding thiazoles **4b−h** in yields ranging from 67% to 96% (entries 1−7). Notably, the aryl group tolerates a halogen atom and a boryl group as the substituents, although the produced halo- and boryl-substituted thiazoles are difficult to synthesize with the previously reported palladium-catalyzed C−H arylation reactions of thiazoles.[6] Whereas 1-cyclohexenyl-substituted triazole **1k** successfully participated in the sequential reaction (entry 9), *n*-propyl-substituted triazole **1l** afforded the product **4k** in 49% yield, probably due to a 1,2-hydride shift occurring with the rhodium carbene complex (entry 10).[21]

A diverse array of thionoesters was also readily prepared from the corresponding carboxylic esters by the reaction with the Lawesson's reagent, and they were reacted with the triazole **1b** (Scheme 2). 2-Aryl-5-phenylthiazoles **4l−t** were obtained in

Scheme 2. Rh(II)-Catalyzed Reaction of 1b with Various *O*-Alkyl Thioates 2[a]



[a]On a 0.20 mmol scale. [b]$TsOH·H_2O$ was used instead of SiO_2.

yields ranging from 58% to 99%. Styryl-substituted thionoester was also effectively converted into the product **4u** in 86% yield. In the case of alkyl-substituted thionoesters, the aromatization process from intermediate 4-thiazolines was slightly more sluggish to afford the products **4v** and **4w** in moderate yields.

The synthetic usefulness of the present reaction was demonstrated by its successful integration into a one-pot procedure which directly started from readily available terminal alkynes **5** (Table 2). First, a solution of **5** (1.0 equiv), mesyl azide (1.0 equiv), and CuTC (5.0 mol %) in chloroform was stirred for 8 h at room temperature, generating 1-mesyl-substituted triazoles **1**. Second, thionoesters **2** (1.5 equiv) and $(^tBuCO_2)_4Rh_2$ (2.0 mol %) were added to the same vessel, which was then heated at 70 °C for 1 h. Finally, acidic silica gel was added to the reaction mixture to promote deprotective aromatization. The corresponding thiazoles **4** were obtained in overall yields ranging from 80% to 85%. Thus, the rhodium-catalyzed annulation reaction in the second step was barely interupted by the copper catalyst employed in the first step. This one-pot procedure saves a significant amount of time and solvents for a workup/purification procedure.[22]

The one-pot procedure was applied to steroidal substrate **6a** and *δ*-tocopherol-derived substrate **6b** (eqs 3 and 4). The

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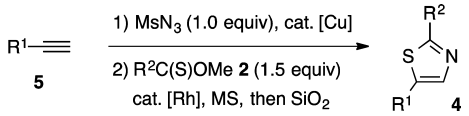
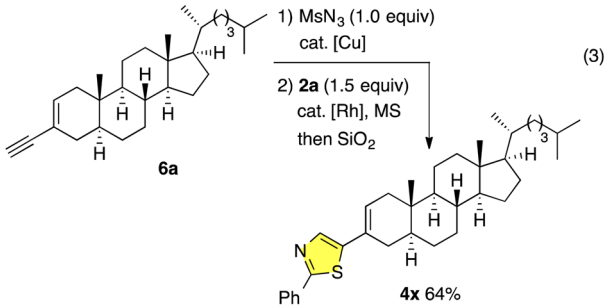
Table 2. One-Pot Synthesis of Thiazoles 4 Starting from Terminal Alkynes[a]

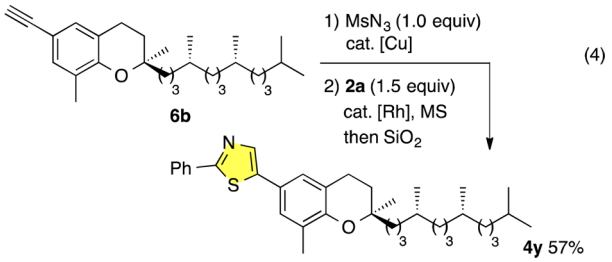


entry	R^1	5	R^2	4	yield (%)[b]
1	Ph-	**5a**	Ph-	**4a**	80
2	*p*-MeO-C_6H_4-	**5b**	Ph-	**4c**	82
3	3-Thienyl-	**5c**	Ph-	**4i**	82
4	Ph-	**5a**	*p*-MeO-C_6H_4-	**4l**	85
5	Ph-	**5a**	*p*-Br-C_6H_4-	**4n**	83

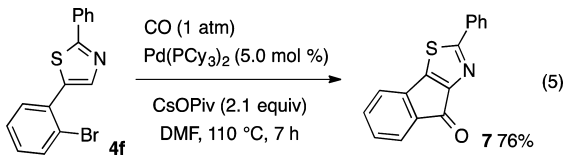
[a]On a 0.20 mmol scale. [b]Isolated yield.

corresponding thiazolyl-substituted derivatives **4x** and **4y** were successfully obtained in 64% and 57% overall yields based on the starting terminal alkynes **6a** and **6b**.



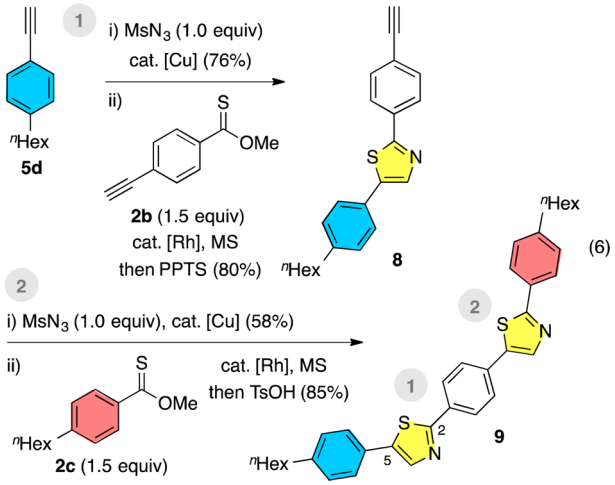


Derivatization of the obtained thiazole was exemplified in eq 5. When the palladium(0)-catalyzed conditions developed by

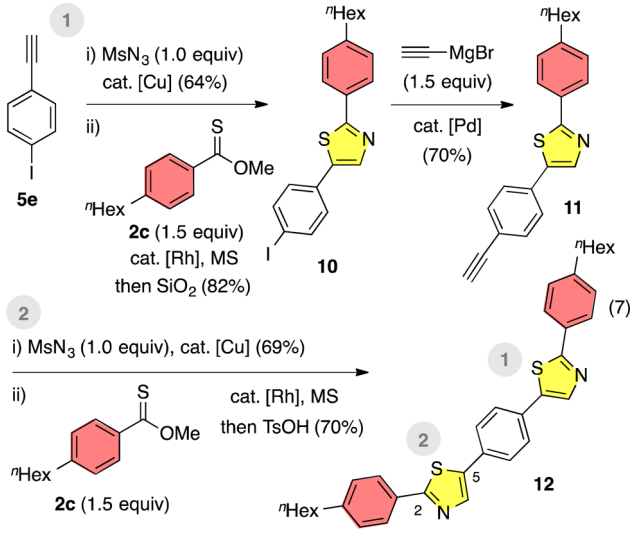


Larock[23] were applied to *o*-bromophenyl-substituted thiazole **4f**, the carbonylative cyclization reaction took place to give 4*H*-indeno[2,1-*d*]thiazole-4-one **7**.

The terminal alkyne-based thiazole synthesis was further extended to an iterative procedure for the synthesis of linear oligomeric arylene compounds. For example, the ethynyl-substituted benzothioate **2b** presents a useful building block for the iterative procedure (eq 6). The first thiazole formation from **5d** and **2b** was carried out in a stepwise manner to furnish ter(arylene) **8** possessing a terminal ethynyl group. Next, the terminal ethynyl group of the ter(arene) **8** was utilized for the second thiazole formation with 4-hexylbenzothioate **2c** to produce the quinque(arylene) **9** consisting of two thiazole and three benzene rings.

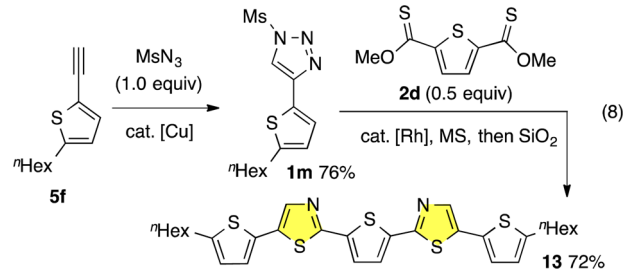


Quinque(arylene) **12** having a different array of two thiazole and three benzene rings was also synthesized (eq 7). Initially, 5-



(4-iodophenyl)thiazole **10** was prepared from **5e** and **2c**, and then a terminal ethynyl group was introduced on the phenyl ring by a palladium-catalyzed coupling reaction,[24] forming **11**. The second thiazole formation was carried out using **11** and **2c** to produce the quinque(arylene) **12**.

Quinque(thiophene/thiazole) oligomers could be efficiently synthesized based on the present thiazole synthesis. The triazole **1m** was prepared from 2-ethynylthiophene **5f** and mesyl azide. Then, thiophene-2,5-bis(carbothioate) **2d** (0.1 mmol) was reacted with **1m** (0.2 mmol). Double annulation took place to afford symmetrical quinque(thiophene/thiazole) oligomer **13** in 72% yield (eq 8).



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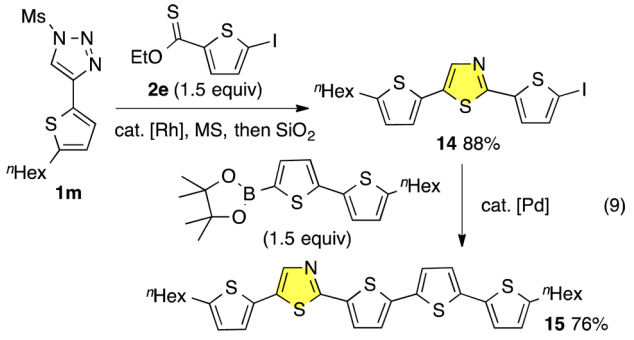
Unsymmetrical quinque(thiophene/thiazole) oligomer **15** was constructed from the same triazole **1m** (eq 9). Initially,



the thiazole formation from **1m** and 5-iodothiophene-2-carbothioate **2e** was carried out to furnish iodo-substituted ter(thiophene/thiazole) oligomer **14**. Then, boryl-substituted bi(thiophene) was reacted with **14** in the presence of a palladium catalyst to produce **15** in 76% yield.[25]

In summary, we have demonstrated that thionoesters can act as the dipolarophiles toward α-imino rhodium(II) carbene complexes and developed a useful method for the synthesis of 2,5-disubstituted thiazoles starting from terminal alkynes. This procedure was successfully applied to late-stage transformation of biorelated derivatives and highly selective synthesis of oligomeric arylene compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00960.

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Notes

The authors declare no competing financial interest.

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