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α-Sulfanyl and α-Selanyl Propadienyl Cations: Regioselective Generations and Cycloadditions with Thioamides and Selemides Controlled by $MeNO_2-H_2O$ System

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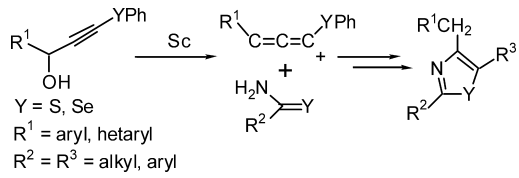
ABSTRACT



α-Sulfanyl and α-selanyl propadienyl cations were easily generated by the catalytic system, scandium triflate-nitromethane-H_2O in the presence of Bu_4NHSO_4, to regioselectively afford the multifunctionalized thiazoles and selenazoles in high yields.

Thiazole and its derivatives are among the most useful hetaryl functional groups and found in many natural products and biologically active compounds.[1] Numerous methods for the preparation of thiazoles have been reported;[2] however, the most widely used method is the Hantzsch thiazole synthesis that uses reactions between α-haloketones and their analogs with thioamides.[3] Despite the modified methods reported recently for the syntheses of thiazoles, novel methods for synthesizing thiazoles are required because of the importance of synthetic thiazole in medicinal and agricultural chemistry.[4]

Recently, we reported scandium-catalyzed carbon−carbon bond forming reactions using 3-sulfanyl and selanyl propargyl alcohols with the soft nucleophiles.[5]

Scandium metals effectively catalyze the generation of propargyl cations through the electron-donating ability of the heteroatom on the terminal acetylene group. Usually, the propargyl cations have been generated either as a complex protected by dicobalt hexacarbonyl[6] or as an allenylidene complex.[7] Our propargylation would be applied to the cycloadditions with thioamide, which serve a convenient

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alternative to the syntheses of thiazoles, because the organosulfanyl and organoselanyl acetylenes can easily react with both nucleophiles and electrophiles.[8] As a preliminary step, we carried out the scandium-catalyzed reactions of the 3-selanylpropargyl alcohol and thiobenzamide give the cycloadducts; the regioselectivity and the positioning of between the nitrogen and sulfur atoms were determined by the X-ray analysis. The crystal data confirmed 4-(*p*-bromobenzyl)-2-phenyl-5-(phenylselanyl)thiazole (Figure 1).

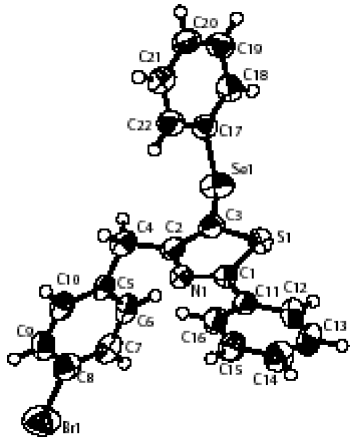
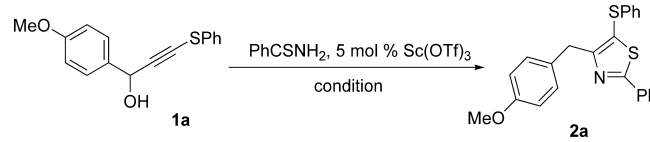


Figure 1. ORTEP drawing of 4-*p*-bromobenzyl-2-phenyl-5-phenylselanylthiazole.

This is a surprising result in that the thiazole was formed from the cycloaddition of the α-phenylselanylpropadienyl cation, not the 3-selanylpropargyl cation. The thiazoles from 3-bromoalk-1-ynes and thioamides are usually obtained through the cycloaddition of propargylic sulfinamide.[9] This unprecedented result would offer a new strategy for the preparations of thiazoles. Herein, we report the scandium-catalyzed generation and cycloaddition of the α-sulfanyl and α-selanyl propadienyl cations with thioamides under optimized phase transfer conditions.

In our initial study, 1-*p*-methoxyphenyl-3-(phenylsulfanyl)prop-2-yn-1-ol (**1a**) was reacted with thiobenzamide under a variety of conditions (Table 1). This led to the following conclusions: scandium triflate in nitomethane ($MeNO_2$) afforded the product **2a** and an increase in the

Table 1. Discovering Reaction Conditions for Scandium-Catalyzed Preparations of 4-(4-Methoxybenzyl)thiazole **2a**



entry	condition[a]	yield (%)
1	$MeNO_2$, rt, 1 h	19
2	$MeNO_2$, reflux, 10 min	52
3	Bu_4NHSO_4 (0.2 equiv), $MeNO_2$, reflux, 10 min	14
4	Bu_4NHSO_4 (0.2 equiv), $MeNO_2$, reflux, 10 min	62
5	Bu_4NHSO_4 (0.5 equiv), $MeNO_2$, reflux, 10 min	34
6	Bu_4NCl (0.2 equiv), $MeNO_2$, reflux, 10 min	47
7	Bu_4NBr (0.2 equiv), $MeNO_2$, reflux, 10 min	46
8	Bu_4NHSO_4 (0.2 equiv), $MeNO_2-H_2O$ (10:1), reflux, 10 min	94
9	DBU (0.1 equiv), $MeNO_2-H_2O$ (10:1), reflux, 10 min	–
10	Bu_4NBF_4 (0.2 equiv), $MeNO_2-H_2O$ (10:1), reflux, 10 min	48
11	Bu_4NHSO_4 (0.2 equiv), $MeNO_2-H_2O$ (5:1), reflux, 10 min	93

[a] Five mol % of scandium triflate was used except in entry 3.

reaction temperature increased the yields (entries 1−2); the additives, such as ammonium salts, gave the desired product in good yields (entries 3−8, 10−11); the addition of water as a cosolvent increased the yield considerably (entries 8−11). The use of DBU as an additive decreased the yield of the product (entry 9). The use of scandium triflate (5 mol %), $MeNO_2-H_2O$ (10:1), Bu_4NHSO_4 (10 mol %) under reflux conditions provided the best yield of this product **2a** (entry 8).

Next, we examined the reaction on the various intermediates bearing the phenylsulfanyl group under the reaction conditions of both method A and B. Most of the reactions carried out using method B ($MeNO_2/H_2O$ = 10:1) resulted in the formation of 2-phenyl and 2-methyltriazoles **2** and **3**. Note that the reaction of 2-thienyl derivative **1g** with thioacetamide gave a mixture of both 2-methyl-5-(phenylsulfanyl)-4-(2-thienylmethyl)thiazole and 2-methyl-4-(phenylsulfanyl)-5-(2-thienylmethyl)thiazole; however, the product by method B gave 2-methyl-5-(phenylsulfanyl)-4-(2-thienylmethyl)thiazole **3g** (Table 2, entry 9).

The phenylselanylpropargyl alcohols **4** with thioamides were also investigated under the same conditions (Method B). We successively carried out the deselanylation of the cycloadducts using MeLi and obtained the thiazoles **5**, **6** and the selenazoles **7** in good to excellent yields (Table 3).

Scheme 1 depicts a catalytic cycle for the thiazole cycloaddition, which involves in situ generation of the α-selanyl propadienyl cation as a reactive species. The propargyl cation **10** is generated from scandium-catalyzed activation and dehydroxylation of the alcohol **8**. Because of the high number of nucleophilicities, the carbon nucleophiles attack the propargyl cation to form the propargylated products.[5] However, nucleophilicity of thioamides is weaker, and therefore, the propargyl cation would isomerize to the

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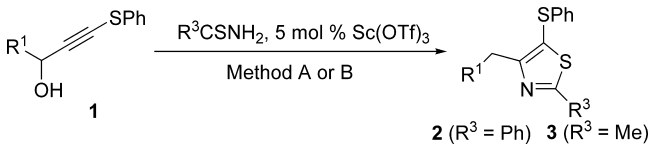
Table 2. Scandium-Catalyzed Cycloadditions of 3-Sulfanyl-propargyl Alcohols **1** with Thioamides

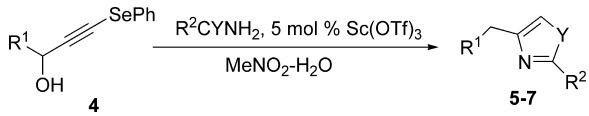


entry	alcohol **1** R^1	yield (%/method)[a]
1	Ph	**2b** (50/A; 86/B)
2	*p*-ClC_6H_4	**2c** (50/A; 84/B)
3	*p*-FC_6H_4	**2d** (quant/B)
4	*p*-BrC_6H_4	**2e** (90/B)
5	1-naphthyl	**2f** (48/A; 93/B)
6	2-thienyl	**2g** (quant/B)
7	*p*-$MeOC_6H_4$	**3a** (84/A; 86/B)
8	*p*-FC_6H_4	**3d** (quant/B)
9	2-thienyl	**3g** (50/A[b]; 84/B)

[a] Method A: $Sc(OTf)_3$(5 mol %), $MeNO_2$, reflux; Method B: $Sc(OTf)_3$(5 mol %), $MeNO_2-H_2O$ (10:1), reflux. [b] 2-Methyl-5-(phenylsulfanyl)-4-(2-thienylmethyl)thiazole/2-methyl-4-(phenylsulfanyl)-5-(2-thienyl-methyl)thiazole = 60:40.

propadienyl cation stabilized by either the sulfur or the selenium atom. The reaction of the propadienyl cation **10′** with thioamides probably gives the propadienylimine intermediate **11**, which easily cyclizes in the 5-exo mode, leading to the product **12**. Tetrabutylammonium hydrogensulfate would effectively act as a scavenger of the eliminated hydroxyl group. In fact, the slow disappearance of the alcohols gave rise to the formations of the Meyer-Schuster rearrangement products resulting from attack of the hydroxyl

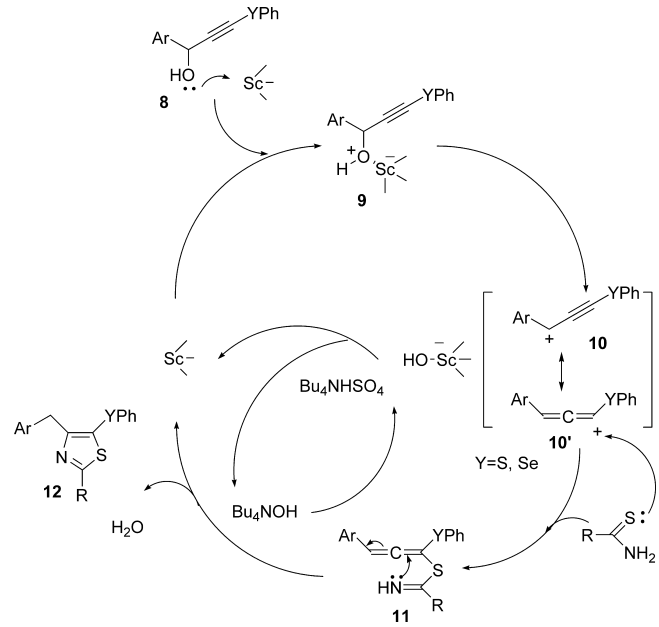
Table 3. Conversion of 3-Selanylpropargyl Alcohols **4** to 4-Arylmethylthiazoles and Selenazoles



entry	alcohol **4** R^1	Y	yield (R^2) (%)[a]
1	*p*-$MeOC_6H_4$	S	**5a** (R^2 = Ph) (63)
2	Ph	S	**5b** (R^2 = Ph) (58)
3	*p*-ClC_6H_4	S	**5c** (R^2 = Ph) (84)
4	*p*-BrC_6H_4	S	**5d** (R^2 = Ph) (67)
5	1-naphthyl	S	**5e** (R^2 = Ph) (86)
6	2-thienyl	S	**5f** (R^2 = Ph) (86)
7	3,4-$(MeO)_2C_6H_3$	S	**5g** (R^2 = Ph) (65)
8	3,4-(methylenedioxy)-C_6H_3	S	**5h** (R^2 = Ph) (84)
9	2,4,6-$Me_3C_6H_3$	S	**5i** (R^2 = Ph) (94)
10	*p*-$MeOC_6H_4$	S	**6a** (R^2 = Me) (99)
11	2-thienyl	S	**6f** (R^2 = Me) (99)
12	*p*-$MeOC_6H_4$	Se	**7a** (R^2 = Ph) (99)
13	2-thienyl	Se	**7f** (R^2 = Ph) (54)
14	2,4,6-$Me_3C_6H_3$	Se	**7i** (R^2 = Ph) (70)
15	*p*-FC_6H_4	Se	**7j** (R^2 = Ph) (78)

[a] 4-Arylmethyllthiazoles and selenazoles were obtained by treatment with MeLi or Bu_3SnH/AIBN then MeLi.

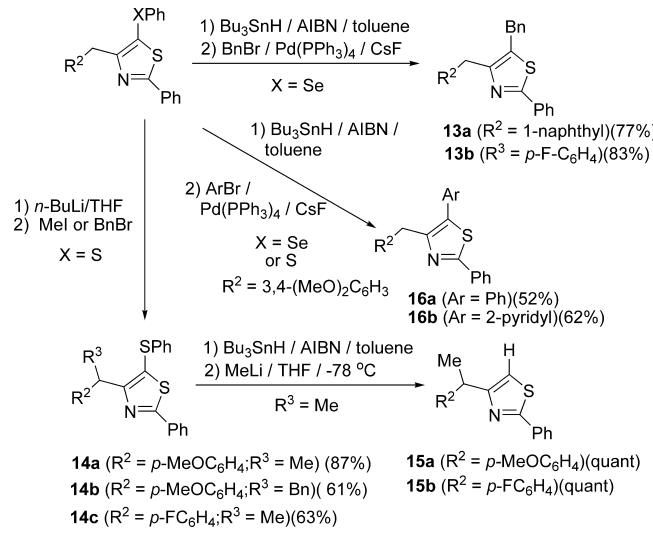
Scheme 1. Tentative Mechanism for Scandium-Catalyzed Cycloaddition



group on the propadienyl cation **10′** even under the conditions of Method B.

We extended the functional transformations of the thiazoles by transmetalations or transition metal-catalyzed arylations (typical results are shown in Scheme 2). The 5-phenylselanylthiazoles easily underwent transmetalation with Bu_3SnH/AIBN to form the 5-tributylstannylated thiazole intermediate. The alkylations with benzyl bromide provided **13a**−**b** in high yields. The lithiations and alkylations of 5-sulfanyl thiazoles gave **14a**−**c** resulting from alkylations at the benzylic carbon. 5-Sulfanyl group of thiazoles underwent cleavage using Bu_3SnH/

Scheme 2. Transformations of the Thiazoles



AIBN then MeLi. 5-Sulfanyl group of thiazoles underwent cleavage using Bu_3SnH/

AIBN followed by treatment with MeLi to form **15a**−**b**. Palladium-catalyzed Stille couplings of thiazoles proceeded via tributylstannylthiazole.

In summary, we have developed a new cycloaddition reaction of the 3-sulphanyl and 3-selanylpropargyl alcohols having thioamides and selenamide with complete regioselectivities, presumably by the effective nitromethane-H_2O-Bu_4NHSO_4 system. Further work in progress is aimed at exploring the synthetic organic reactions using α-sulphanyl and selanyl propadienyl cations as intermediates.

Supporting Information Available: Typical experimental procedures, spectral data for all of the new compounds, the copies for ^1H and ^{13}C NMR spectral data of **3c**, **5g**, **6b**, **7b**, **7d**, **14c**, **15b** and X-ray crystallographic data (X-ray data for 4-*p*-bromobenzyl-2-phenyl-5-phenylselanylthiazole). This material is available free of charge via the Internet at http://pubs.acs.org.

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