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[3+3] Cycloaddition

Synthesis of Thiazinoimidazoles by Lewis Acid–Catalyzed [3+3] Cycloaddition Reactions of Propargyl Alcohols with 2-Mercaptoimidazoles

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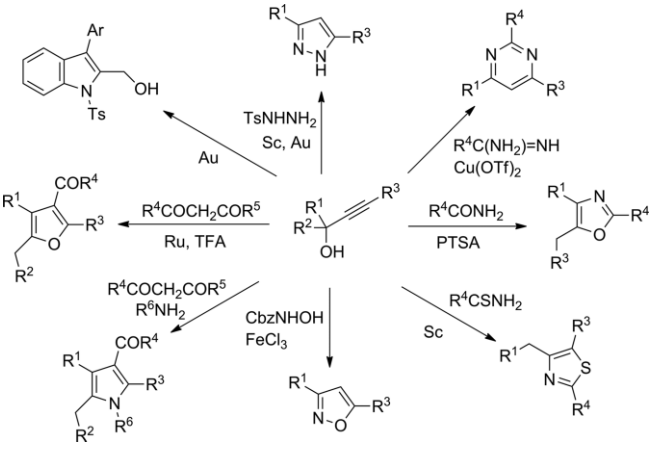
Abstract: The unique ytterbium-catalyzed generation of sulfur- and selenium-substituted propargylic and allenic cations and their reactions with 2-mercaptoimidazole derivatives were described. The regioselective [3+3] annulation reactions proceeded to give a wide variety of S,N-acetal-containing bicyclic and tricyclic thiazinoimidazoles in good to high yields. Treatment of thiazinoimidazoles with LDA readily underwent ring contraction to afford thiazolobenzimidazoles. Deselenenylation and successive functionalization broaden the scope of accessible thiazinoimidazoles.

Introduction

Propargyl alcohol is a good tool for the generation of both propargyl and allenic cations, which were extensively investigated to achieve the regioselective carbon–carbon, carbon–oxygen, carbon–nitrogen, and carbon–sulfur bond formation reactions (Scheme 1). Nicholas reactions using alkyne–cobalt complexes are one of the most well-known processes and dramatically enhance their stabilities by dicobalt–hexacarbonyl complex.[1] Two decades' progress in this field has explored the catalytic processes for propargyl and allenic substitutions and their further transformations from useful alcohols or their synthetic equivalents.[2] In particular, Watts and Müller independently provided Nicholas-type intermediates stabilized by ferrocene[3] and chromium complexes.[4] Dramatic progress in the catalytic propargylations has been achieved by Uemura and Nishibayashi's protocols using ruthenium–allenilidene complexes.[5]



Scheme 1. Propargyl alcohols as a good tool for a wide variety of heterocycles.

Results and Discussion

Recent advances enable catalytic propargylation and allenylation, which are excellent tools for heterocycle synthesis.[6] Usually, most alcohols act as two carbon electrophiles in the [3+2] annulations for five-membered heterocycles, such as furans,[7] pyrroles,[8] isoxazoles,[9] indoles,[10] pyrrazoles,[11] oxazoles,[12] and thiazoles.[13] In general, the six-membered ring formations are only relevant cyclization models, except the rarer example, the [3+3] annulation for pyrimidine synthesis by copper triflate-catalyzed process.[14] We previously reported the Lewis acid-catalyzed cyclization of sulfur- and selenium-substituted propargyl alcohols with thioamides and selenamides.[13] The excellent sulfur- and selenium-functional groups on the alkyne termini can effectively stabilize the corresponding cations and react with thioamides and selenamides, respectively, to provide thiazoles and selenazoles through their intermolecular [3+2] cycloaddition reactions. In this process, sulfur-substituted propargyl alcohols could act as a carbon electrophile (C=C$^+$ synthon) in Lewis acid-catalyzed cycloaddition reactions with thioamides as a S–C–N synthon. However, our continuing study in this field leads to a new finding that the propargyl alcohols could also play an important role as a carbon electrophile (C=C–C$^+$ syn-

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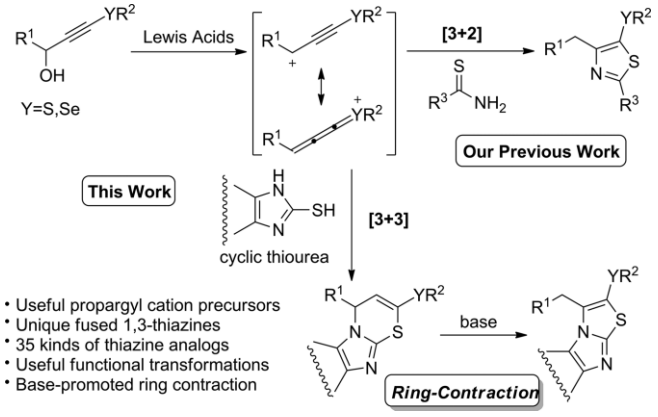
thon). Here we report the Lewis acid-catalyzed [3+3] annulation reaction of sulfur- and selenium-substituted propargyl alcohols with three types of 2-mercaptoimidazoles as novel fused 1,3-thiazines as pharmacore[15] (Scheme 2).

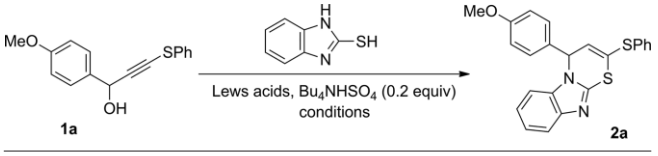


Scheme 2. Cycloadditions of propargyl cations stabilized by sulfur- and selenium-functional groups with 2-mercaptoimidazoles.

We first prepared the sulfur-substituted propargyl alcohols **1a**–**j** and **1r**–**t** from the nucleophilic addition reactions of aromatic and heteroaromatic aldehydes and ketones according to our previous methods.[11a,11b,13a,13b,16] The selenium analogs **1k**–**p** were also prepared by almost the same method. In accordance with our previous thiazole synthesis,[13a,13b] we selected a suitable partner **1a** for the Lewis acid- catalyzed reaction with 2-mercaptobenzimidazole: scandium triflate as the Lewis acid and nitromethane as the solvent, at 100 °C (entry 1, Table 1). The reaction was completed in 2.5 h, and the product **2a** was obtained in relatively good yield. The ^{1}H NMR spectrum of **2a** showed two doublets at δ = 6.16 and 6.52 (J = 4.8 Hz) ppm due to the vicinal protons of thiazine ring. The fact shows that the Lewis acid-catalyzed cycloaddition reaction of sulfur-substituted propargyl alcohols with 2-mercaptoimidazole would undergo [3+3] annulation rather than usual [3+2] annulation reactions to give 4-(4-methoxyphenyl)-2-(phenylthio)-4*H*-[1,3]thiazino[3,2-*a*]benz-imidazole (**2a**). As the unique structure of thiazinoimidazole was found to be rarer, we screened the suitable reaction conditions: solvents and Lewis acids (Table 1). From the results of entries 2–5, both DCE and nitromethane were found to be suitable for the cycloaddition reactions. Lanthanoide metals like ytterbium and lanthanum triflate effectively played an important role in the thiazine synthesis. However, common Lewis acids such as boron trifluoride diethyl ether and tin(II) triflate were not suitable for the cycloadditions. Furthermore, tetrabutylammonium hydrogensulfate is necessary for the completion of the reactions.

With the optimized reaction conditions in hand, we next examined the substrate scope of sulfur-substituted propargyl alcohols **1**, as shown in Table 2. The study on the substituent

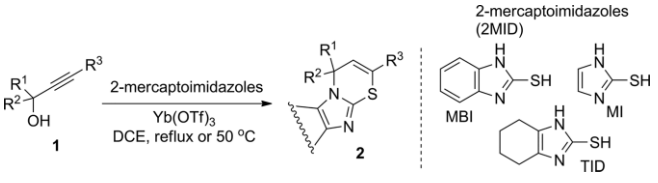
Table 1. Screening of reaction condition.



entry	solvent	Lewis acids (equiv.)	T [°C], time	Product (% yield)[b]
1	$MeNO_2$[a]	$Sc(OTf)_3$ (0.1)	100, 2.5 h	81
2	$MeNO_2$	$Sc(OTf)_3$ (0.1)	100, 15 min	67
3	DCE	$Sc(OTf)_3$ (0.1)	85, 10 min	84
4	dioxane	$Sc(OTf)_3$ (0.1)	100, 10 min	67
5	toluene	$Sc(OTf)_3$ (0.1)	100, 10 min	54
6	DCE	$Yb(OTf)_3$ (0.1)	85, 10 min	95
7	DCE	BF_3Et_2O (0.2)	85, 10 min	24
8	DCE	$La(OTf)_3$ (0.1)	85, 2 h	74
9	DCE	$Sn(OTf)_2$ (0.1)	85, 10 min	50
10	DCE	$Mg(OTf)_2$ (0.1)	85, 3 h	mixture

[a] H_2O was added. [b] Yields of isolated product.

Table 2. Substrate scope.



entry		Alcohol R^1	R^2	R^3	2MID	Products[a] (% yield)
1	**1b**	Ph	H	PhS	MBI	**2b** (81)
2	**1c**	$^pFC_6H_4$	H	PhS	MBI	**2c** (70)
3	**1d**	$^pClC_6H_4$	H	PhS	MBI	**2d** (66)[b]
4	**1e**	$^pBrC_6H_4$	H	PhS	MBI	**2e** (73)[b]
5	**1f**	3,4-($MeOC_6H_3$)	H	PhS	MBI	**2f** (87)
6	**1g**	2-furyl	H	PhS	MBI	**2g** (89)
7	**1h**	2-thienyl	H	PhS	MBI	**2h** (91)
8	**1i**	$^oMeOC_6H_4$	H	PhS	MBI	**2i** (96)
9	**1j**	$^mMeOC_6H_4$	H	PhS	MBI	**2j** (93)
10	**1k**	3,4(OCH_2O)C_6H_3	H	PhS	MBI	**2k** (77)
11	**1l**	$^pMeOC_6H_4$	H	PhSe	MBI	**2l** (70)
12	**1m**	$^pClC_6H_4$	H	PhSe	MBI	**2m** (54)
13	**1n**	$^oMeOC_6H_4$	H	PhSe	MBI	**2n** (96)
14	**1o**	$^pBrC_6H_4$	H	PhSe	MBI	**2o** (56)[b]
15	**1p**	2-furyl	H	PhSe	MBI	**2p** (84)
16	**1q**	2-thieyl	H	PhSe	MBI	**2q** (81)
17	**1r**	$-(CH_2)_4-$		PhS	MBI	**2r** (48)
18	**1s**	$-(CH_2)_5-$		PhS	MBI	**2s** (85)
19	**1t**	$-(CH_2)_6-$		PhS	MBI	**2t** (87)
20	**1u**	$O_2NC_6H_4$	H	PhSe	MBI	**2u** (10)
21	**1v**	Ph	H	Ph	MBI	**2v** (–)
22	**1a**	$^pMeOC_6H_4$	H	PhS	MI	**3a** (92)
23	**1c**	$^pFC_6H_4$	H	PhS	MI	**3c** (70)
24	**1d**	$^pClC_6H_4$	H	PhS	MI	**3d** (61)
25	**1e**	$^pBrC_6H_4$	H	PhS	MI	**3e** (85)
26	**1f**	3,4-$(MeO)_2C_6H_3$	H	PhS	MI	**3f** (79)
27	**1i**	$^oMeOC_6H_4$	H	PhS	MI	**3i** (87)
28	**1l**	$^pMeOC_6H_4$	H	PhSe	MI	**3l** (92)
29	**1n**	$^oMeOC_6H_4$	H	PhSe	MI	**3n** (67)
30	**1r**	$-(CH_2)_4-$		PhS	MI	**3r** (49)
31	**1s**	$-(CH_2)_5-$		PhS	MI	**3s** (83)
32	**1t**	$-(CH_2)_6-$		PhS	MI	**3t** (73)
33	**1w**	$-(CH_2)_5-$		PhSe	MI	**3w** (72)
34	**1a**	$^pMeOC_6H_4$	H	PhS	TID	**4a** (66)
35	**1h**	2-thienyl	H	PhS	TID	**4h** (31)
36	**1i**	$^pMeOC_6H_4$	H	PhSe	TID	**4l** (75)

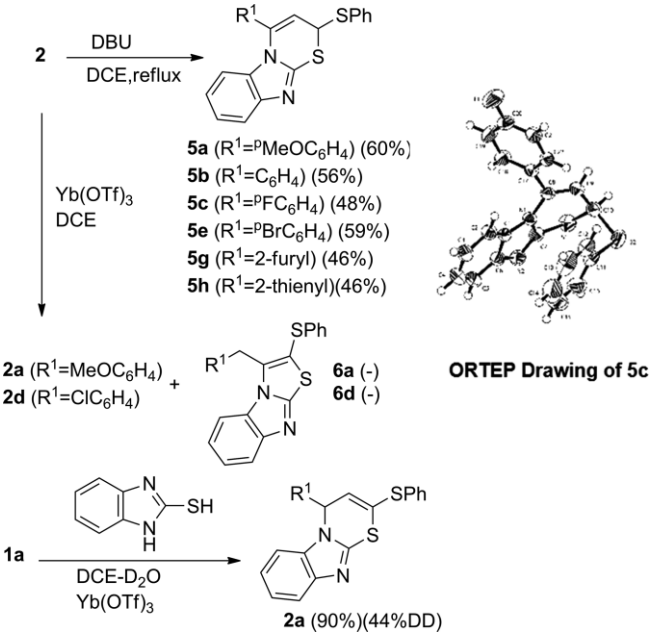
[a] Yields of isolated product. [b] The reaction was performed at 50 °C.

on propargyl alcohols revealed that phenyl- and *p*-fluorophenylpropargyl alcohols afforded thiazines **2b**–**c** in high yields (entries 1 and 2). However, the similar reactions of *p*-chlorophenyl alcohol **1d** gave a complex mixture. The reaction of *p*-bromophenyl derivatives **2e** has given almost the same result. Therefore, we performed the same reactions of both **1d**–**e** at 50 °C succeeded to give the thiazine **2d**–**e**; however, the yields of products were moderate (entries 3 and 4).

When 3,4-dimethoxyphenyled alcohol **1f** underwent regioselective cycloaddition to lead the exclusive formation of thiazinoimidazole **2f** (entry 5). Heteroaromatic analogs, such as furan and thiophene, could give **2g**–**h** in high yields (entries 6 and 7). *o*-and *m*-substituted arylthiazines **2i**–**j** were also obtained in excellent yields (entries 8 and 9). Moreover, the bicyclic heteroaromatic 3,4-methylenedioxyphenyl derivative **2k** was also obtained in 77 % yield (entry 10). Next, we examined the reactions of 3-phenylselenopropargyl alcohols **1l**–**q** with 2-mercaptobenzoimidazole under similar reaction conditions (entries 11–15). Most of 2-(phenylseleno)thiazines **2l**–**q** were also obtained in good yields. The similar tendency is that the halo-substituted phenyl propargyl alcohols **1m** and **1o** would provide thiazine **2m** and **2o** formation in moderate yields (entries 23 and 24). Unfortunately, the nitrophenyled propargyl alcohol **1u** gave product **2u** in low yield (entru 20). To elucidate the sulfur- and selenium-stabilizing effects in the thiazine formation, we performed the reaction of 1,3-diphenyl propargyl alcohol **1v** with 2-mercaptobenzoimidazole; however, any cycloadduct was not observed (entry 21). The quaternary alcohols, such as 1-phenylsulfanylcycloalkanols **1r**–**w**, succeeded in giving spirothiazine derivatives **2r**–**w** in moderate to high yields (entries 30–33).

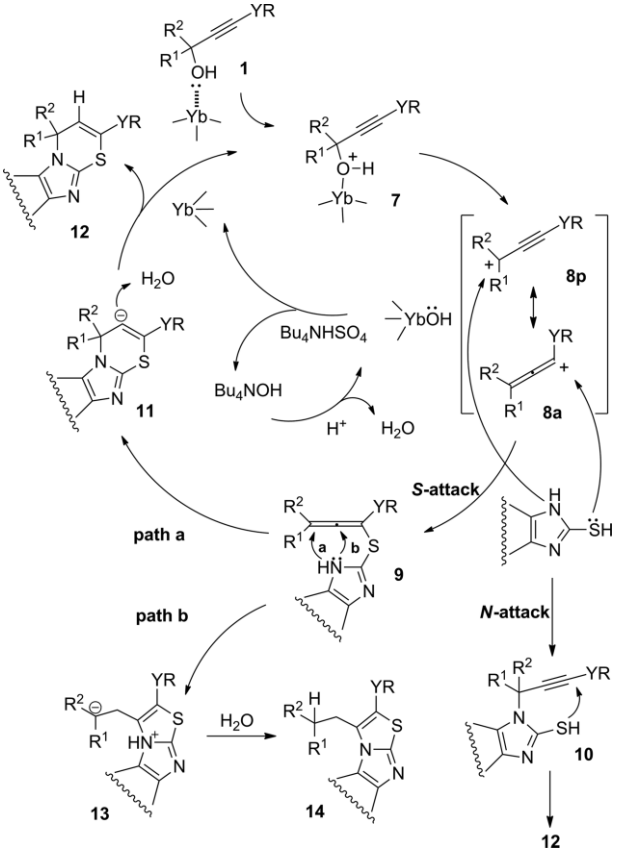
To confirm both the structure of thiazines and the mechanism for [3+3] cycloaddition reaction of sulfur- and selenium-substituted propargyl alcohols with 2-mercaptoimidazoles, we performed some experiments, and the results were shown in Scheme 3. Base-promoted isomerization of 2*H*-[1,3]thiazino-[3,2-*a*]benzimidazole to 4*H*-derivatives **5a**–**h** was observed. Fortunately, the single X-ray analysis of **5c**, which was obtained as pure crystals, disclosed the unique fused ring system as shown in the ORTEP drawing. Furthermore, we conducted the ytterbium-catalyzed reactions of both **2a** and **2d** in order to confirm the possibility of either isomerization or ring contraction; however, most of thiazines were recovered. When we performed the [3+3] annulation reaction of **1a** in [D_3]nitromethane/D_2O, thiazine **2a** deuterated at 3-position was obtained in 44 % DD. Based on these results and our previous mechanistic investigations for the thiazole synthesis, we could not determine whether the first addition of 2-mercaptoimidazole toward the cationic intermediates would occur either between the allenic cation and the sulfur atom of 2-mercaptoimidazoles or between the propargylic cation and the nitrogen atom of 2-mercaptoimidazoles.[13b] However, the intramolecular cyclization and the successive protonation would proceed the thiazine derivatives from these experimental results.

The plausible mechanism for the formation of products is shown in Scheme 4. Dehydration of sulfur- and selenium-substituted propargyl alcohol **1** proceeds via **7** to give the propargyl cation **8p**, and its tautomer allenyl cation **8a** is stabilized by α-



Scheme 3. Mechanistic investigation.

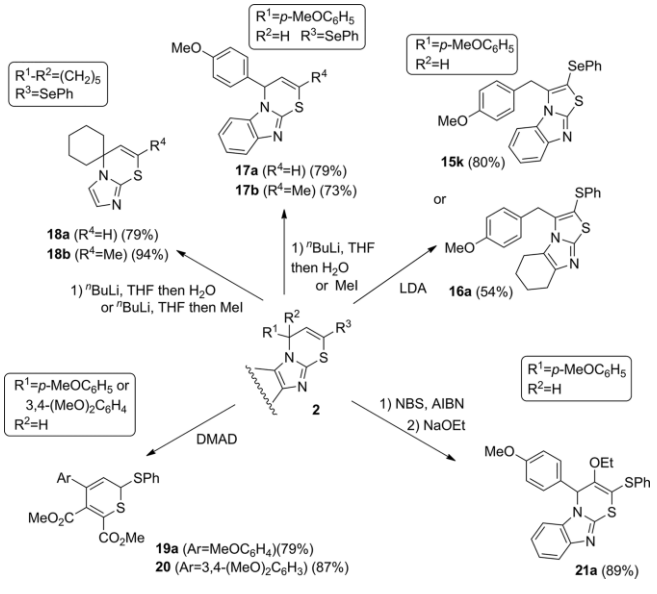
sulfur and selenium atoms and reacts with 2-mercaptoimidazole in a regioselective manner to give *S*-allenylimidazo-2-yl intermediate **9** or *N*-propargyl-2-mercapto-imidazole **10**. The intramolecular cyclization of either **9** or **10** would proceed via the 6-*endo-dig* mode and the successive protonation to give



Scheme 4. Proposed mechanism.

the thiazinoimidazole **11**. However, we previously confirmed that the thiazole synthesis using sulfur- and selenium-substituted propargylic cations with thioamides or selenamides would proceed via the sulfur attack of thioamides toward the allenyl carbon of **8a** confirmed by the deuterium experiments, except the 1,1-diarylpropargyl alcohols. On the other hand, the 5-*exo*-mode cyclization of **9** and protonation of **13** give the thiazole **14**. We have not isolated the thiazoles in this annulation system, and the reactions would proceed via the 6-*endo-dig* mode to give the thiazine derivatives because of the angles of the second attack of fixed 2-mercaptoimidazoles. Whether this thiazine formation could not be accompanied by the thiazole formation in the reactions of both *p*-chloro- and *p*-bromopropargyl alcohols with 2-mercaptobenzimidazole remains unclear. Tetrabutylammonium hydrogensulfate would play an important role in the ytterbium-catalyzed generation of propadienyl cations.

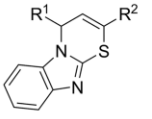
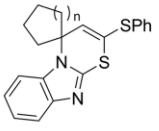
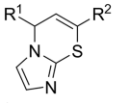
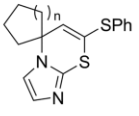
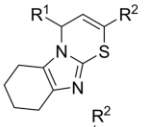
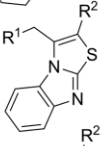
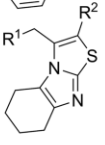
The synthetic utilization of thiazines was examined using benzimidazole derivative **2** as shown in Scheme 5. We have already described above the base-promoted isomerization of thiazines and further investigated the reactions with other bases, such as LDA or *n*BuLi. The reaction of **2k** with LDA surprisingly afforded the ring-contracted thiazole **15k**. The unique ring contraction proceeded in the treatment of 6,7,8,9-tetrahydro-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole (**4a**) with LDA. The transmetalation of 2-seleno-1,3-thiazine with *n*BuLi proceeded, and the successive hydration gave **17a**. The successive methylation with iodomethane afforded **17b** in good yield. The useful selenium-substituted spirothiazines were also converted into the no-selenium-thiazines **18a**–**b** by the sequential transmetalation-alkylation process. Our unique [3+3] annulation reactions produced a new type of two and three ring-fused thiazines. Furthermore, some transformations afforded another functionalized thiazines **21a**. Surprisingly, the reactions with DMAD afforded the thiopyrans **19a** and **20** accompanied by debenzoimidazolylation.



Scheme 5. Transformation of 2.

The antiproliferative activity of these new compounds against HCT-116 colon tumor cells was assessed, and the data are shown in Table 3. At the treatment of 100 μM analogs, the **3a**, **3s**, **3t**, and **16a** almost inhibited cell viability completely. The analog **2h** decreased tumor cell viability to the half level and indicated the antiproliferative activity with lower concentration.

Table 3. Antiproliferative activities of synthesized thiazine and thiazole derivatives against HCT-116 cells.

compound		HCT-116 cells viablity (%)	
		10 μM	100 μM
	**2a**; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	105.2	101.4
	2b; R^1=C$_6$H$_5$, R^2=SPh	106.1	63.7
	2c; R^1=^{p}FC$_6$H$_4$, R^2=SPh	98.8	71.8
	2d; R^1=^{p}ClC$_6$H$_4$, R^2=SPh	103.8	25.4
	2e; R^1=^{p}BrC$_6$H$_4$, R^2=SPh	97.1	95.3
	2f; R^1=3,4-(MeO)$_2$C$_6$H$_3$, R^2=SPh	101.2	107.6
	2g; R^1=2-furyl, R^2=SPh	86.0	57.9
	2h; R^1=2-thienyl, R^2=SPh	56.3	42.8
	**2l**; R^1=^{p}MeOC$_6$H$_4$, R^2=SePh	151.4	148.2
	2r; n=1	99.2	33.5
	2s; n=2	105.2	95.1
	2t; n=3	104.3	99.5
	**3a**; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	103.3	6.3
	3l; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	100.9	45.7
	**3r**; n=1	70.3	32.5
	3s; n=2	85.2	7.1
	3t; n=3	106.0	9.8
	**4a**; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	102.3	43.1
	4h; R^1=2-thienyl, R^2=SPh	88.4	75.3
	4l; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	104.7	72.2
	**5b**; R^1=^{p}MeOC$_6$H$_4$, R^2=SePh	100.4	54.8
	**16a**; R^1=^{p}MeOC$_6$H$_4$, R^2=SPh	89.6	3.2

Conclusions

In summary, we have disclosed a new Lewis acid-catalyzed [3+3] annulation reaction of sulfur- and selenium-substituted propargyl alcohols with 2-mercaptoimizaoles. The protocol is an exclusive formation of thiazines and shows a wide variety of substrate scope. Three types of 2-mercatoimidazoles of the sulfur- and selenium-substituted propargyl alcohols succeeded to afford 35 kinds of thiazines in good to high yields. We are currently investigating the syntheses of other heterocycles using the Lewis acid-catalyzed sulfur- and selenium-substituted propargyl alcohols.

Experimental Section

2a: To a 1,2-dichloroethane (0.600 mL) solution of **1a** (20.0 mg, 0.074 mmol), 2-mecaptobenzimidazole (22.0 mg, 0.148 mmol) and tetrabutylammonium hydrogensulfate (5.00 mg, 0.015 mmol) was added ytterbium triflate (4.00 mg, 0.007 mmol) at room temperature. The reaction mixture was heated at 85 °C for 10 min. The almost same procedure as that of entry 1 and purification by preparative TLC gave **2a** (28 mg, 95 %) as white powders. Mp. 166–168 °C (CH_2Cl_2/*n*-hexane), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.76 (3H, s, MeO), 6.16 (1H, d, *J* = 4.8 Hz, CH), 6.52 (1H, d, *J* = 4.8 Hz, CH), 6.85 (2H, d, *J* = 8.9 Hz, ArH), 7.03 (1H, d, *J* = 8.3 Hz, ArH), 7.06–7.09 (1H, m, ArH), 7.17–7.22 (3H, m, ArH), 7.29–7.32 (3H, m, ArH), 7.42 (1H, d, *J* = 6.9 Hz, ArH), 7.63 (1H, d, *J* = 7.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.2 (q), 59.2 (d), 109.8 (d), 114.7 (d × 2), 118.6 (d), 122.2 (d), 122.7 (d), 123.0 (s), 126.2 (d), 127.6 (d × 2), 128.1 (d), 129.3 (d × 2), 130.7 (d × 2), 132.1 (s), 133.7 (s), 143.5 (s), 145.1 (s), 159.8 (s). IR (ATP): $\tilde{\nu}$ = 3053, 3003, 2955, 2928, 2835, 1710, 1609, 1583, 1510, 1476, 1440, 1392, 1351, 1335, 1305, 1253, 1218, 1175, 1153, 1113, 1032, 958, 906, 856, 831, 740, 689, 568, 528 cm^{-1}; EIMS *m/z* 402 (M^+), 293 (M^+ – SPh). Anal. Calcd for $C_{23}H_{16}N_2OS_2$ + 1/4H_2O: C, 67.94; H, 4.59; N, 6.89; found C, 67.89; H, 4.49; N, 6.86.

CCDC 1898519 (for **5c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Keywords: Thiazines · [3+3] Annulation · Cycloaddition · Mercaptoimidazoles · Ring contraction

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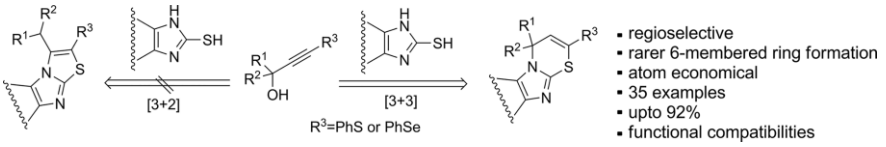
[3+3] Cycloaddition



Fused thiazinoimidazole synthesis from the sulfur- and selenium-substituted propargyl alcohols with 2-mercaptoimidazoles were reported. The protocol is utilized for [3+3] annulation reactions of a wide variety of propargyl alcohols with three types of 2-mercaptoimidazoles. The reactions were regioselective, atom economical, and versatile. Further transmetalation and the successive hydration and alkylation could provide the more useful thiazines.

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