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Synthesis of 1,2,4-dichalcogenazoles by the reaction of 6*H*-1,3,5-oxachalcogenazines with elemental chalcogen

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Abstract—A series of 1,2,4-dichalcogenazoles were synthesized by the reaction of 6*H*-1,3,5-oxachalcogenazines with elemental chalcogen through the plausible pathway involving in situ generation of 1,3-chalcogenaza-1,3-butadienes and the subsequent reaction with chalcogen species. Synthetic utilities of 1,2,4-dichalcogenazoles were also explored.

Studies on heterocyclic compounds containing sulfur and nitrogen atoms are fascinating areas of current research due to their versatile applications. In particular, compounds possessing dichalcogenazole ring offer increasing interests in the field of pharmaceutical and fundamental research.[1] However, intensive research is going on in the field of five-membered heterocycles having nitrogen atom. Although heterocycles having disulfur-moiety together with nitrogen atom have great demand due to their frequent appearance in living system, but this field has been studied the least. Burger reported a synthesis of 1,2,4-dichalcogenazoles by taking the advantage of strong stabilizing functionality, trifluoromethyl group, using 2*H*-1,3-thiazetes as precursors.[2a] This method suffers from the lack of generality in respect of substrates and requiring prolonged reaction period, in some cases, it takes 4–5 weeks. On the other hand, the synthetic utilities of this novel ring system still remain to be explored. Therefore, little is known about the structure and reactivities of 1,2,4-dichalcogenazoles due to the lack of a general method of synthesis.

In the course of our studies on reactive chalcogenocarbonyl building blocks, we reported a generation of 1,3-chalcogenaza-1,3-butadienes (**A**, **B**) through thermal cycloreversion of 6*H*-1,3,5-oxachalcogenazines (**1**, **2**), respectively.[2b] We obtained 3*H*-1,2,4-dichalcogenazoles **3** and **5** as byproducts during our studies on 6*H*-1,3,5-oxachalcogenazines (**1**, **2**).[2b]

It was envisaged that 1,2,4-dichalcogenazoles **3**–**7** would be synthesized through the reaction of in situ generated **A** or **B** with elemental chalcogen as shown in Scheme 1.

In accordance with the expectation, we succeeded to synthesize **3**–**6** in moderate to excellent yields by the heating of **1** or **2** with elemental chalcogen in toluene. Now, we wish to report a novel method for the synthesis of a series of 1,2,4-dichalcogenazoles **3**–**6** from **1** or **2** via in situ generation of **A** or **B** and will describe some synthetic utilities of these compounds.

6*H*-1,3,5-Oxachalcogenazines **1**, **2** were prepared by treating a thioamide or a selenoamide with an aliphatic aldehyde and $BF_3{\cdot}OEt_2$ according to the reported procedures.[2b,3]

Screening experiment for the synthesis of **3** from **1** by using elemental sulfur, P_2S_5, or Lawesson's reagent was suggested to be elemental sulfur (chalcogen) as chalcogen source.

The reaction of **1a**–**e** with elemental sulfur in toluene refluxing temperature afforded 3*H*-1,2,4-dithiazoles **3a**–**e** in moderate to excellent yields. The physical data including MS, IR, ^{1}H NMR, and ^{13}C NMR, as well as elemental analysis were fully consistent with the structure of 3*H*-1,2,4-dithiazoles **3**. The results of thermolysis

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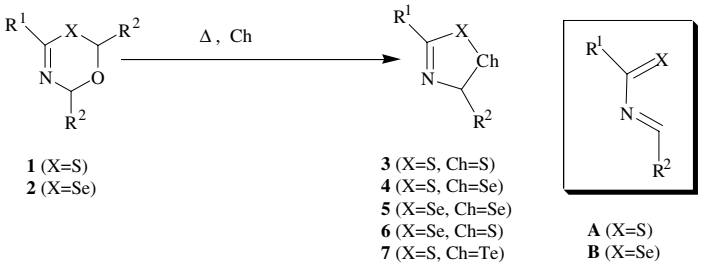


Scheme 1.

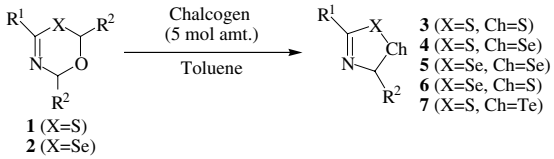
and thiation reactions of **1a–e** are summarized in Table 1. When **1a** was heated in the absence of sulfur, only a trace amount of **3a** was afforded along with recovery of substrate (entry 1). It is thought that thermal cycloreversion of **1a** generates heterodiene **A**, which might cause further fragmentation to give sulfur species, and the subsequent reaction of heterodiene **A** with the released sulfur species to afford compound **3a**. When **1e** having CH_3 group at C-2 and C-6 positions was heated with elemental sulfur, expected compound **3e** was formed in moderate yield along with unidentified compounds (entry 6).

The reaction of **1** with elemental selenium in toluene refluxing temperature afforded the expected 3*H*-1,2,4-thiaselenazoles **4** in moderate to excellent yields as shown in Table 1 (entries 7–10). However, in the case of entries 8 and 10, the unexpected 3*H*-1,2,4-dithiazoles **3** were also found along with **4**. An independent reaction of **4a** with elemental sulfur (2 mol amt.) at toluene refluxing temperature for 15 h afforded **3a** in quantitative yield. This result might suggest that minor compound **3a** was formed by the reaction of **1a** with elemental selenium, via primary formation of **4a** followed by the exchanging reaction of selenium in **4a** ring with sulfur species,[4,5] which was assumed to be generated from **A**.

The reaction of **2a** with elemental selenium in toluene at 98 °C afforded 3*H*-1,2,4-diselenazoles **5a** in 72% yield (Table 1, entry 11). The physical data including MS, IR, ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR, as well as elemental analysis were fully consistent with the structure of 3*H*-1,2,4-diselenazoles **5a**.

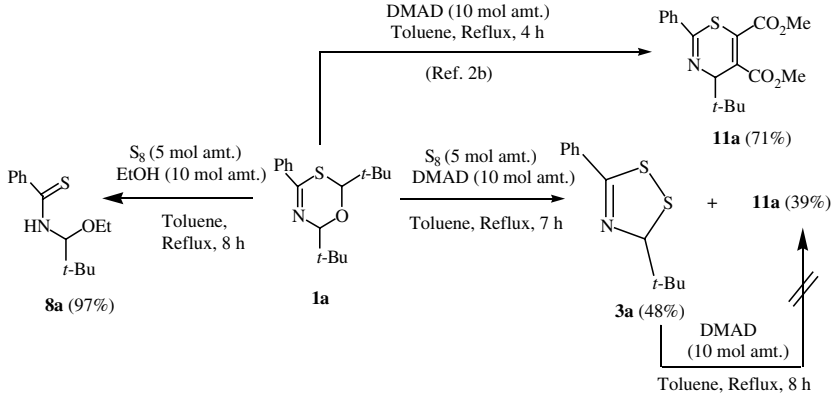
The reaction of **2a** with elemental sulfur in toluene at 98 °C afforded an inseparable mixture of 3*H*-1,2,4-dithiazole **3a**, 3*H*-1,2,4-diselenazole **5a** and plausible 5*H*-1,2,4-thiaselenazole **6a** (Table 1, entry 12). The most likely structure of **6a** was suggested through the analysis of ^{1}H NMR and mass spectral data of the mixture. The chemical shifts of the likely structure **6a** are probably δ 1.14 (9H, s) and 6.08 (1H, s). On the other hand, chemical shifts of those of isomer **4a** are δ 1.12 (9H, s)

Table 1. Synthesis of 1,2,4-dichalcogenazoles by the reaction of 6*H*-l,3,5-oxachalcogenazines with chalcogen atom



Entry	Substrate			Chalcogen	Temperature (°C)	Time (h)	Yield (%)[a]					
	R^1	R^2					**3**	**4**	**5**	**6**	**7**	Recovery
1	C_6H_5	*t*-C_4H_9	**1a**	—[b]	Reflux	15	Trace	—	—	—	—	98
2	C_6H_5	*t*-C_4H_9	**1a**	S	Reflux	15	88	—	—	—	—	0
3	*p*-ClC_6H_4	*t*-C_4H_9	**1b**	S	Reflux	25	91	—	—	—	—	6
4	*p*-FC_6H_4	*t*-C_4H_9	**1c**	S	Reflux	25	89	—	—	—	—	7
5	*p*-$CH_3OC_6H_4$	*t*-C_4H_9	**1d**	S	Reflux	15	98	—	—	—	—	0
6	C_6H_5	CH_3	**1e**	S	Reflux	5	48	—	—	—	—	0
7	C_6H_5	*t*-C_4H_9	**1a**	Se	Reflux	15	0	98	—	—	—	0
8	*p*-ClC_6H_4	*t*-C_4H_9	**1b**	Se	Reflux	15	20	44[c]	—	—	—	0
9	*p*-FC_6H_4	*t*-C_4H_9	**1c**	Se	Reflux	15	0	97	—	—	—	0
10	*p*-$CH_3OC_6H_4$	*t*-C_4H_9	**1d**	Se	Reflux	15	15[c]	63[c]	—	—	—	0
11	C_6H_5	*t*-C_4H_9	**2a**	Se	98	12	—	—	72	—	—	0
12	C_6H_5	*t*-C_4H_9	**2a**	S	98	12	50[c]	0	20[c]	30[c]	—	0
13	C_6H_5	*t*-C_4H_9	**1a**	Te	Reflux	15	33	—	—	—	0	Trace
14	*p*-$CH_3OC_6H_4$	*t*-C_4H_9	**1d**	Te	Reflux	15	36	—	—	—	0	Trace

[a] Isolated yield.
[b] In the absence of chalcogen atom.
[c] NMR yield.



Scheme 2.

and 6.88 (1H, s), but isomer **4a** was not observed in the ^{1}H NMR spectrum of this mixture. Moreover, the coupling constant between the carbon atom at C-3 position and the selenium atom of **4a** was $^1J_{C-Se} = 63$ Hz, implying that the ring system of **4a** is 3*H*-1,2,4-thiaselenazole. In addition, the mass spectra of the mixture containing **6a** showed a parent ion peak (m/z) at 285 assigned to **6a**, and all of these results suggest the structure of **6a**.

Surprisingly, when **1a** or **1d** was reacted with elemental tellurium in toluene refluxing temperature, the expected 3*H*-1,2,4-thiatellurazole **7a** or **7d** could not be detect, besides the unexpected product **3a** or **3d** was formed in moderate yield (Table 1, entries 13 and 14). However, the thermolysis of **1** in the absence of sulfur atom only gave a trace amount of **3a** (entry 1), assuming that compound **7** was transiently formed, followed by the reaction with liberated sulfur species (from heterodiene **A**) to afford compound **3** through tellurium–sulfur exchanging.

Generally, heterodienes, 1,3-chalcogenaza-1,3-butadienes (**A**, **B**), are generated through thermal cycloreversion of appropriate precursors at elevated temperature. However, synthesis or generation of such building blocks at low temperature is of great demand in synthetic organic chemistry. We found a new route for the generation of heterodienes **A** and **B** at room temperature by using 1,2,4-dichalcogenazoles **3**–**6** as potential precursors.

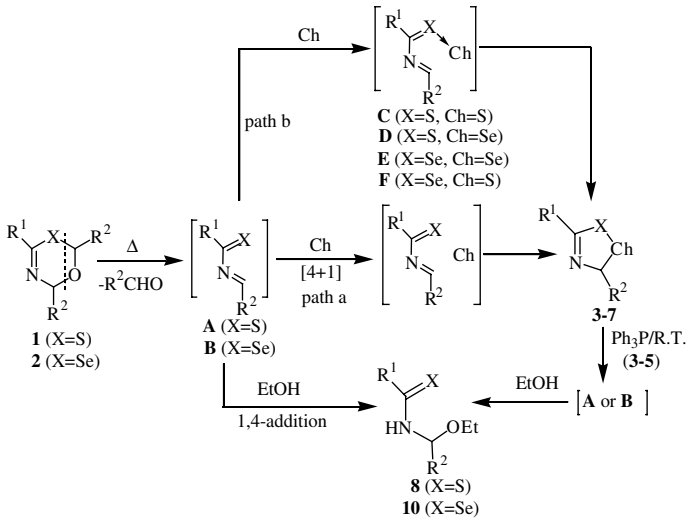
It was expected that 1,3-thiaza-1,3-butadienes **A** would be generated through the extrusion of sulfur atom (S-2) from 3*H*-1,2,4-dithiazoles **3a** ring system. The reaction of **3a** with Ph_3P (1.0 mol amt.) in the presence of EtOH in CH_2Cl_2 at room temperature afforded **8a** in 98% yield, 1,4-adduct of heterodiene **A** with EtOH, along with Ph_3P=S in 72% yield.

The reaction of **4a** with Ph_3P (1.0 mol amt.) in the presence of EtOH at room temperature for 1 h afforded **8a** in 85% yield, the 1,4-adduct of heterodiene **A** with EtOH, along with Ph_3P=Se in 69% yield. It is demonstrated that both compounds **3** and **4** are new precursors for the generation of heterodiene **A** at low temperature. Moreover, generation of **A** along with Ph_3P=Se in the reaction of **4** with Ph_3P strongly suggests that the location of sulfur–selenium unit should be 1,2-position in 3*H*-1,2,4-thiaselenazole **4** ring system. When compound **5a** was treated with Ph_3P (1.0 mol amt.) in the presence of EtOH at room temperature for 1 h gave **10a** in 78% yield, the 1,4-adduct of heterodiene **B** with EtOH, along with Ph_3P=Se in 68% yield.

We have already reported that the heating of **1a** with an excess amount of dimethylacetylenedicarboxylate (DMAD) in toluene refluxing temperature afforded **11a** in 71% yield, [4+2] cycloadduct of heterodiene **A** with DMAD.[2b] Reaction of **1a** with elemental sulfur (5 mol amt.) in the presence of EtOH in toluene refluxing temperature resulted in the formation of compound **8a** in 97% yield, the 1,4-adduct of heterodiene **A** with EtOH, and no compound **3a** was observed. On the other hand, treatment of **1a** with elemental sulfur (5 mol amt.) in the presence of DMAD gave **3a** in 48% yield along with **11a** in 39% yield. However, when **3a** was independently heated with DMAD in toluene refluxing temperature for 8 h, no reaction occurred. This result ruled out the possibility of the opening of 1,2,4-dichalcogenazoles ring only by heating (Scheme 2).

By considering the above results suggesting the generation of heterodiene **A** by a series of the trapping experiment of **1a** with EtOH or DMAD, it can be rationalized that the necessity of heterodienes **A** or **B** and chalcogen species for the synthesis of 1,2,4-dichalcogenazoles **3**–**7** should be essential. A plausible formation pathway of **3**–**7** involving [4+1]-type cycloaddition (path a)[2a] through the reaction of in situ generated **A** or **B** with chalcogen atom is proposed. However, another pathway involving transient generation of intermediate **C** or **D** or **E** or **F** and their subsequent ring closure (path b)[6] can not exclude out at this time as shown in Scheme 3.

In conclusion, we have developed a novel method for an efficient synthesis of a wide range of 1,2,4-dichalcogenazoles **3**–**7** from 6*H*-1,3,5-oxachalcogenazines **1** and **2** by treating with elemental chalcogen. In addition, a new method for the generation of heterodienes **A** and **B** at low temperature using 1,2,4-dichalcogenazoles **3**–**5** as precursors has also been developed. Further studies on



Scheme 3. Plausible formation pathway of compounds **3**–**10**.

the mechanistic approach are in progress in our laboratory.

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