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Silica gel-promoted synthesis of 3,4,5-triaryltetrahydro-1,4-thiazine derivatives from β,β′-dichloro sulfides and aromatic amines

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Abstract—A novel and efficient synthesis of 3,4,5-triaryltetrahydro-1,4-thiazine derivatives by treatment of β,β′-dichloro sulfides, 2:1 adducts of alkenes and sulfur dichloride, with aromatic amines in the presence of silica gel is described. The silica gel can be easily recovered and reused in up to four consecutive reactions without any significant decrease in product yield.

Inorganic solid-promoted syntheses have recently attracted considerable attention because of their environmental compatibility, high selectivity and reactivity, simplicity of operation, and low cost.[1] Several classes of inorganic solids are commonly used in these heterogeneous reactions, and include silica gel, alumina, and clay.[2] We previously reported on the inorganic solid-promoted syntheses of heterocyclic compounds such as oxathiane and dithiane derivatives from β,β′-dichloro sulfides.[3]

β,β′-Dichloro sulfides are reliable acceptors of a wide variety of heteroatom nucleophiles owing to the reactive episulfonium intermediates that are produced by the neighboring sulfur atom participation.[4] Therefore, they are frequently utilized in the synthesis of sulfur containing heterocyclic compounds.[5]

1,4-Thiazine ring is one of such heterocycles and is known to play an important role in pigments, dyestuffs, and biologically active substances.[6] Among them, 4-aryltetrahydro-1,4-thiazine is an interesting and important skeleton found in compounds with pharmacological activity and, for example, several compounds containing this moiety are known to exhibit potent antimycobacterial and antitumor activity.[7] Typically, tetrahydro-1,4-thiazine derivatives are prepared by the reaction of β,β′-dichloro sulfides with amines only in the presence of more than 1 equiv of inorganic base,[5a–c] and the transformation without any base has not so far been reported. Although these methods are applied to the synthesis of 4-alkyltetrahydro-1,4-thiazines, they cannot be successfully used for the synthesis of 4-aryl derivatives, because of the simultaneous production of diamino sulfides and difficulties associated with product purification.[8] Therefore, a more efficient and convenient synthetic method for preparing 4-aryltetrahydro-1,4-thiazines would be desirable. Herein, we wish to report on a novel synthesis of 4-aryl-1,4-thiazines from β,β′-dichloro sulfides by utilizing an inorganic solid, which is easily recovered from the reaction mixture and can potentially be reused.

β,β′-Dichloro sulfides **1** were simply prepared as a mixture of diastereomers in high yields through the addition of SCl_2 to olefins.[3a] We previously succeeded in the

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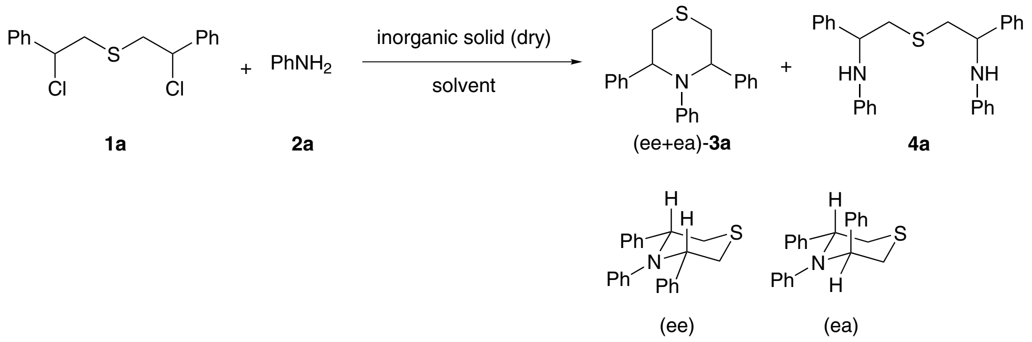
synthesis of oxathiane and dithiane derivatives by the reaction of β,β′-dichloro sulfides with water and hydrogen sulfide, respectively, on inorganic solids under mild reaction conditions. Consequently, in the presence of aqueous ammonia, this type of reaction would be expected to lead to the formation of a thiazine ring. However, the treatment of β,β′-dichloro sulfide **1a** with aqueous ammonia on silica gel afforded a complex mixture. On the other hand, detailed studies of the reaction of **1a** with aniline (**2a**) indicated that 3,4,5-triaryltetrahydro-1,4-thiazine **3a** is produced in good yield (Scheme 1), and the results are summarized in Table 1. It is noteworthy that the reaction of **1a** with **2a** in the absence of silica gel gave only a small amount of **3a**, while the presence of silica gel led to a smooth reaction, affording **3a** in 68% isolated yield along with diamino sulfide **4a** as a byproduct (entries 1 and 2).[9] Product **3a** was formed as a mixture of diastereomers (ee)-**3a** and (ea)-**3a** and their structures were determined by spectral analysis. As shown in Table 1, the yield of **3a** was influenced to a considerable extent by the reaction conditions. The use of sodium carbonate, alumina, and montmorillonite K10 (mont. K10) instead of silica gel did not give good yields of **3a** (entries 3–5). Toluene and chlorobenzene were found to be more favorable solvents for this reaction than DMF and diethoxyethane (entries 2 and 6–8). The best yield of **3a** was obtained when 3 equiv of **2a** was used (entries 2, 9, and 10). An increase in the reaction temperature from 80 to 100 °C and the reaction time from 0.5 to 3 h also led to improved yields (entries 2, 11, and 13), and a further increase in the temperature or prolonged heating had a negative effect on the yield (entries 12 and 14).

The silica gel-promoted reaction of β,β′-dichloro sulfides **1** with various aromatic amines **2** was then examined under the optimized conditions (Scheme 2, Table 2). The reaction was successfully applied to some β,β′-dichloro sulfides **1a**–**c** and several aromatic amines **2a**–**e** to afford the corresponding 3,4,5-triaryltetrahydro-1,4-thiazines **3a**–**g** in good yields (entries 1–7). In particular, 3,5-diphenyl-4-*o*-fluorophenyltetrahydro-1,4-thiazine (**3e**), which is a part of the skeleton of antimycobacterials,[7a] was obtained in 58% from **1a**



Scheme 1.

Table 1. Synthesis of tetrahydrothiazine **3a** from β,β′-dichloro sulfide **1a** and aniline[a]

Entry	Inorganic solid	Solvent	**2a** (equiv)	Temp (°C)	Time (h)	Yield[b] (%)	
						3a	**4a**
1[c]	—	Toluene	3	100	3	5	<55
2	SiO_2	Toluene	3	100	3	71[d]	14
3[c]	Na_2CO_3[e]	Toluene	3	100	3	8	34
4[c]	Al_2O_3	Toluene	3	100	3	18	62
5	Mont. K10	Toluene	3	100	3	36	26
6	SiO_2	PhCl	3	100	3	68[d]	11
7	SiO_2	DMF	3	100	3	40	31
8	SiO_2	$(EtOCH_2)_2$	3	100	3	43	41
9[c]	SiO_2	Toluene	2	100	3	62	7
10	SiO_2	Toluene	4	100	3	49	33
11	SiO_2	Toluene	3	80	3	33	50
12	SiO_2	Toluene	3	105	3	59	15
13	SiO_2	Toluene	3	100	0.5	50	33
14	SiO_2	Toluene	3	100	5	66	11

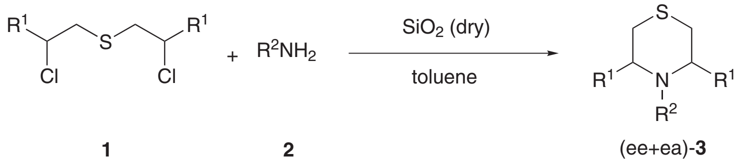
[a] β,β′-Dichloro sulfide (**1a**, 0.5 mmol) was treated with aniline in a solvent (5 mL) in the presence of an inorganic solid (1 g), which was dried at 180 °C for 2 h under reduced pressure.

[b] NMR yields.

[c] Recovery of **1a**; entry 1: <22%, entry 3: 38%, entry 4: 3%, entry 9: 2%.

[d] Isolated yields; entry 2: 68%, entry 6: 67%.

[e] 0.5 mmol.



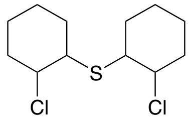
Scheme 2.

Table 2. Silica gel-promoted synthesis of tetrahydrothiazines **3**[a]

Entry	**1**	R^1	**2**	R^2	**3**	Yield (%)	ee/ea
1	**1a**	Ph	**2a**	Ph	**3a**	68	1.4
2	**1a**	Ph	**2b**	4-MeC_6H_4	**3b**	72	1.1
3	**1a**	Ph	**2c**	4-$MeOC_6H_4$	**3c**	64	1.2
4	**1a**	Ph	**2d**	4-ClC_6H_4	**3d**	69	1.8
5	**1a**	Ph	**2e**	2-FC_6H_4	**3e**	58	2.6
6	**1b**	4-MeC_6H_4	**2a**	Ph	**3f**	70	1.5
7	**1c**	4-ClC_6H_4	**2a**	Ph	**3g**	73	1.1

[a] β,β′-Dichloro sulfide (**1**, 0.5 mmol) was treated with aromatic amines (1.5 mmol) in a solvent (5 mL) in the presence of a dried inorganic solid (1 g) at 100 °C for 3 h (except for an amine in entry 3: 1.0 mmol, time in entries 5 and 6: 1 h).

and **2e** (entry 5). However, neither the reaction of **1a** with *n*-butylamine nor that of bis(2-chlorocyclohexyl) sulfide (**1d**) with **2a** gave cyclic products, and β,β′-diamino sulfides were produced as the main products in both reactions.



1d

The activity of the recovered silica gel, used as the promoter, was then examined. Silica gel was easily separated from reaction mixtures by filtration followed by washing with a 2 vol % solution of triethylamine in chloroform. After the first experiment, the recovered silica gel was subjected to a second run using the same substrates (**1a**, **2a**, and toluene). As shown in Table 3, the silica gel could be reused at least three times without any loss in activity or product yield (Table 3).[10]

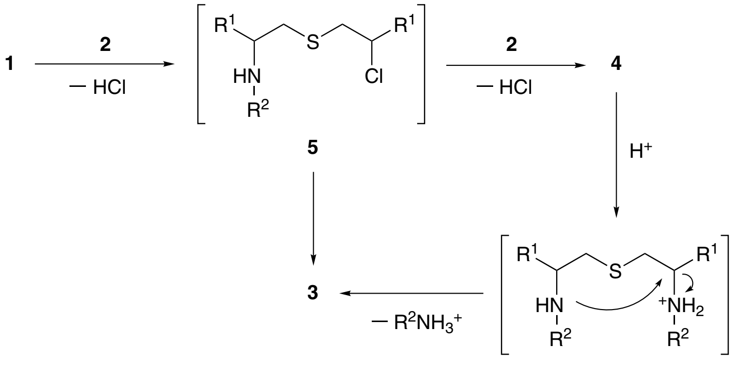
Table 3. Reaction of β,β′-dichloro sulfide **1a** with **2a** in the presence of recycled silica gel[a]

Cycle	1	2	3	4
Yield of **2a** (%)[b]	71 (68)	70	68	71 (71)

[a] **1a** (0.5 mmol) was treated with **2a** (1.5 mmol) in toluene (5 mL) at 100 °C for 3 h in the presence of the recovered silica gel, which was dried at 180 °C for 2 h under reduced pressure.

[b] NMR yields. In parentheses, isolated yields (%) are given.

We previously demonstrated that the conversion of β,β′-dichloro sulfides to oxathiane derivatives on silica gel proceeds via the acid-accelerated cyclization of β,β′-dihydroxy sulfide. Based on the finding that acid accelerates the reaction, the present reaction pathway was examined. When **4a** was treated with tifluoromethanesulfonic acid (1 equiv) in toluene at 100 °C for 3 h, **3a** was produced in 44% NMR yield (Eq. 1). This suggests that hydrogen chloride, generated in situ, plays an important role in the cyclization of **4a** to **3a**. In addition, as described above, in the absence of silica gel, the starting material was recovered (Table 1, entry 1), indicating that silica gel promotes the nucleophilic substitution of **1a** with **2a**. Thus, the transformation of **1** into **3** proceeds via the cyclization of monoamino sulfides **5** or diamino sulfides **4**, and the reactions proceed smoothly on the surface of the silica gel (Scheme 3).



Scheme 3.

$$\mathbf{4a} \xrightarrow[\text{toluene}]{CF_3SO_3H} \underset{44\%}{\mathbf{3a}} \qquad (1)$$

In summary, 3,4,5-triaryltetrahydro-1,4-thiazine derivatives can be effectively synthesized from readily available β,β′-dichloro sulfides and aromatic amines using silica gel as a promoter. The silica gel-promoted method permits the direct synthesis of the sterically hindered tetrahydro-1,4-thiazine ring from β,β′-dichloro sulfides, which is difficult to achieve using conventional methods. The notable features of the present procedure are cleaner reaction profiles, ready recycling of the promoter, and relatively high yields of products.

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9. 3,4,5-Triaryltetrahydrothiazine derivatives **3a**–**g**; general procedure: A 100 mL three-necked flask was charged with silica gel (1 g) and heated at 180 °C for 2 h under reduced pressure to remove traces of water. To the dried silica gel was added a solution of β,β′-dichloro sulfides **1** (0.5 mmol) in toluene (5 mL) and amine (1.5 mmol). The mixture was then stirred at 100 °C for 3 h. The reaction mixture was filtered on a Buchner funnel and the silica gel was washed with chloroform containing triethylamine (2 vol % $NEt_3/CHCl_3$, 20 mL). The combined filtrate was washed with an aqueous solution of NaOH (1 N, 20 mL) and the crude reaction products were extracted from the aqueous layer with chloroform (20 mL). The combined organic layer was dried over anhydrous sodium carbonate, the drying agent was removed by filtration, and the solvent was removed by evaporation. After purification by flash chromatography on silica gel eluting with ethyl acetate/hexane, **3** was obtained as a mixture of diastereomers [(ee)-**3** and (ea)-**3**]. 3,4,5-Triphenyltetrahydro-1,4-thiazine [(ee+ea)-**3a**]: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.70$ (m, 2H, ee), 3.09 (dd, 2H, $J = 5.0$, 13.0 Hz, ea), 3.23 (dd, 2H, $J = 10.6$, 13.6 Hz, ee), 3.45 (dd, 2H, $J = 3.7$, 13.0 Hz, ea), 4.39 (dd, 2H, $J = 2.0$, 10.6 Hz, ee), 5.28 (t, 2H, $J = 4.3$ Hz, ea), 6.57 (d, 2H, $J = 7.9$ Hz, ea), 6.6–7.4 [m, 28H (15+13), ee+ea]. ^{13}C NMR (75 MHz, $CDCl_3$, ee+ea): $\delta = 31.47$, 35.69, 58.70, 69.73, 117.14, 118.66, 124.50, 126.99, 127.01, 127.04, 127.69, 127.94, 127.97, 128.41, 128.63, 141.59, 142.88, 149.11, 150.14. MS (EI, 70 eV, ee+ea): m/z (%) = 331 (M^+, 53), 181 (100), 104 (17), 77 (22).
10. Procedure for recycling of silica gel: A 100 mL three-necked flask was charged with silica gel (1 g) that had been recovered from the former run and heated at 180 °C for 2 h under reduced pressure to remove traces of water. To the dried silica gel was added a solution of β,β′-dichloro sulfide **1a** (0.5 mmol) in toluene (5 mL) and aniline (1.5 mmol). The mixture was then stirred at 100 °C for 3 h. The reaction mixture was filtered on a Buchner funnel and the silica gel was washed with chloroform containing triethylamine (2 vol % $NEt_3/CHCl_3$, 20 mL). The filtered and washed silica gel was used in the next run. The work-up and purification follow the methods described in the general procedure.