Stereoselective Synthesis of 2,4-Disubstituted Thiochromans Using the Supported Reagent System 'Na_2CO_3/SiO_2–PPA/SiO_2'

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Abstract: A simple and efficient method has been developed for the stereoselective synthesis of 2,4-disubstituted thiochromans from arylthiols and α,β-unsaturated aldehydes by using an acid- and a base-supported reagent system, Na_2CO_3/SiO_2–PPA/SiO_2. Michael addition of arylthiol to α,β-unsaturated aldehydes was promoted by Na_2CO_3/SiO_2, and then the product was cyclized in the presence of PPA/SiO_2.

Key words: stereoselective synthesis, thiochroman, supported reagents

The thiochroman ring system is very attractive, because a variety of thiochromans possess biological activity. For instance, thiochroman-6-acetic acid has anti-inflammatory, antipyretic and analgesic activities, and 4-substituted aminothiochromans are active as antidepressants, antihypertensives and agents against angina paints, etc.[1] In general, thiochromans were synthesized via Claisen rearrangement of allyl phenyl sulfide[2] and acid-catalyzed intramolecular cyclocondensation of thiol and β-arylthio aldehyde which are synthesized from arylthiol and α,β-unsaturated aldehyde under basic conditions.[3] Jafarzadeh et al.[4] and Ishino et al.[5] synthesized these thiochromans directly from arylthiols and α,β-unsaturated aldehydes under acidic conditions. These methods made it possible to shorten the two-step reactions, but the neutralization of the reaction mixture in order to obtain pure products could not be avoided. Recently, we developed a silica gel supported polyphosphoric acid (PPA/SiO_2) as a heterogeneous acid catalyst for organic synthesis.[6] The reaction using PPA/SiO_2 has some advantages: PPA/SiO_2 can be separated easily from the reaction mixture; recovered PPA/SiO_2 can be reused after drying; the filtrate need not be neutralized after removing the catalyst by filtration. In continuation of our work using PPA/SiO_2, we found out that both PPA/SiO_2 and silica gel supported sodium carbonate (Na_2CO_3/SiO_2) coexist in the same vessel without neutralization, and benzothiophenes were synthesized from the reaction of arylthiol and α-haloketone using PPA/SiO_2–Na_2CO_3/SiO_2 in the same vessel.[7] In this reaction, Na_2CO_3/SiO_2 promotes the reaction of arylthiol and α-haloketone to give α-sulfenyl ketone, and PPA/SiO_2 catalyzes intramoleculer cyclocondensation of α-sulfenyl ketone. Now, a significant improvement of the stereoselectivity has been achieved for a variety of organic reactions by the use of supported reagents or by the adsorption of substrates onto the surface of an inorganic solid.[8] Herein, we report the stereoselective synthesis of 2,4-disubstituted thiochromans using supported reagents Na_2CO_3/SiO_2–PPA/SiO_2.

First, we investigated a catalytic system for the synthesis of thiochromans **3aa** from *p*-toluenethiol (**1a**) and croton aldehyde (**2a**). For instance, when a mixture of **1a** (4.2 mmol), **2a** (2 mmol) and PPA (0.3 g) was stirred in 1,2-dichloroethane at 80 °C for 4 hours, **3aa** was obtained in 42% yield (Table 1). On the other hand, in the reaction using PPA/SiO_2[9] instead of PPA, the yield of **3aa** (%) increased along with a small amount of by-product **4**. The reaction did not occur without the catalyst. The structure of **4**, 1,1,3-tris(4-methylphenylthio)butane, was confirmed by spectroscopic means using NMR, IR and by mass spectrometry. Because of acidic reaction conditions, compound **4** was formed. Therefore Na_2CO_3/SiO_2[10] was added to the reaction mixture in order to prevent the formation of **4**. In the coexistent system of Na_2CO_3/SiO_2 and PPA/SiO_2, the reaction gave **3aa** in 74% yield, and compound **4** was not detected. We tried to optimize the reaction conditions for the reaction using Na_2CO_3/SiO_2–PPA/SiO_2.

The optimum amount of PPA on silica gel for the reaction was investigated. Using a large amount of PPA loaded onto silica gel, the yield of **3aa** decreased, whereas the yield increased with a higher amount of PPA. PPA/SiO_2 (20 wt%) was the most suitable catalyst for the intramolecular cyclocondensation. In order to determine the optimum conditions for the synthesis of **3aa**, molar ratio of reagents, reaction time and temperature were investigated. When the reaction was carried out using 1.25 g of Na_2CO_3/SiO_2, the yield was the same as in the reaction using 2.0 g of Na_2CO_3/SiO_2. However, in the reaction using less than 1.0 g of Na_2CO_3/SiO_2, the yield of **3aa** decreased, and a small amount of **4** was obtained. The use of a large amount of PPA/SiO_2 did not affect the yield. The rate of the intramolecular cyclocondensation was significantly affected by the reaction temperature. When the reaction was carried out at less than 70 °C, the intra-

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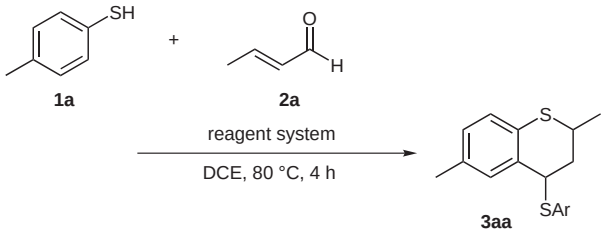
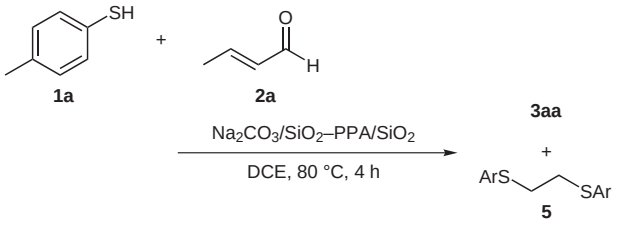
Table 1 Preparation of **3aa** with Various Reagent Systems[a]



Entry	Reagent system	Yield of **3aa** (%)[b]
1	None	0
2	PPA	42
3	PPA/SiO_2	67
4	Na_2CO_3/SiO_2–PPA/SiO_2	74

[a] In all reactions were used 2 mmol of **2a**, 4.2 mmol of **1a**, 0.3 g of PPA, 3.0 mmol of Na_2CO_3 and 15 mL of 1,2-dichloroethane.
[b] Yields were determined by GLC.

molecular cyclocondensation did not proceed at all, but Michael addition of **1a** to **2a** occurred. A shorter reaction time resulted in a decreased yield, but long reaction time and higher reaction temperature did not affect the yield. From the results of these experiments, all reactions were carried out using 2 mmol of **2**, 4.2 mmol of **1**, 1.25 g of Na_2CO_3/SiO_2 (1.5 mmol/g) and 3.0 g of PPA/SiO_2 (20 wt%).



Scheme 1

Table 2 Preparation of **3aa** in Various Solvents[a]

Entry	Solvent	Yield of **3aa** (%)[b]
1	Hexane	73[c]
2	Cyclohexane	76
3	Chloroform	60[c]
4	Benzene	80
5	Toluene	80
6	Monochlorobenzene	86
7	Butanol	4

[a] In all reaction were used 2 mmol of **2a**, 4.2 mmol of **1a**, 1.25 g of Na_2CO_3/SiO_2 (1.5 mmol/g), 3 g of PPA/SiO_2 (20 wt%) and 15 mL of solvent.
[b] Yield were determined by GLC.
[c] A small amount of **4** was observed.

However, when 1,2-dichloroethane was used as a solvent under these conditions, a small amount of 1,2-bis(4-methylphenylthio)ethane (**5**) was formed as by-product (Scheme 1). Compound **5** was formed in the reaction of 1,2-dichloroethane with **1a** in the presence of Na_2CO_3/SiO_2. Therefore we examined another suitable solvent in which **5** was not formed. The results are shown in Table 2. The yield in aromatic solvents was higher than that in aliphatic solvents. Compound **4** was observed in the reaction products when hexane and chloroform were used as solvents (entries 1 and 3). Compound **3aa** was obtained in only 4% yield when a polar solvent such as butanol was used (entry 7). A series of thiochromans was synthesized by using various combinations of **1** and **2**.[11,12] The results are summarized in Table 3. All thiochromans were synthesized in moderate to high yield except for the reaction using 3-methyl-2-butenal. In the reaction with 3-methyl-2-butenal, a large amount of the starting material was recovered (entries 5, 10 and 15). The yield did not increase even if the reaction was carried out using a large amount of Na_2CO_3/SiO_2 or at high reaction temperature.

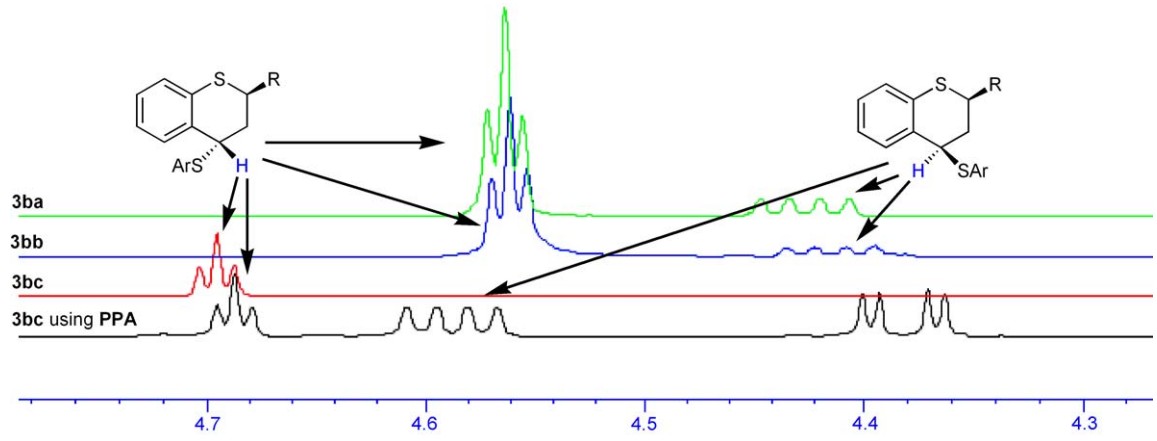
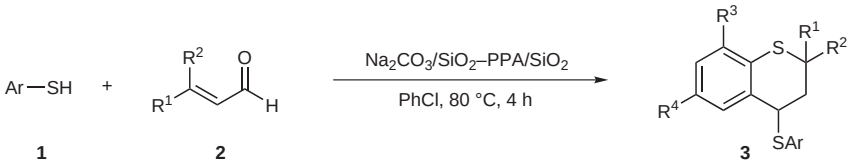


Figure 1 ^1H NMR spectra of compounds **3ba**–**3bc**

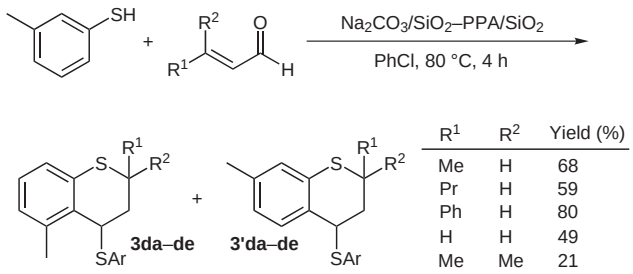
Table 3 Preparation of **3** from **1** and **2** Using Na_2CO_3/SiO_2–PPA/SiO_2[a]



1 **2** **3**

Entry	Ar	R^1	R^2	R^3	R^4	Product	Selectivity (%) (*trans*-isomer)	Yield (%)[b]
1	*p*-MeC_6H_4	Me	H	H	Me	**3aa**	90.9	83
2	*p*-MeC_6H_4	Pr	H	H	Me	**3ab**	96.2	76
3	*p*-MeC_6H_4	Ph	H	H	Me	**3ac**	>99.9	63
4	*p*-MeC_6H_4	H	H	H	Me	**3ad**	–	83
5	*p*-MeC_6H_4	Me	Me	H	Me	**3ae**	–	39
6	Ph	Me	H	H	H	**3ba**	80.0	64
7	Ph	Pr	H	H	H	**3bb**	84.7	73
8	Ph	Ph	H	H	H	**3bc**	>99.9	88
9	Ph	H	H	H	H	**3bd**	–	56
10	Ph	Me	Me	H	H	**3be**	–	30
11	*o*-MeC_6H_4	Me	H	Me	H	**3ca**	87.7	71
12	*o*-MeC_6H_4	Pr	H	Me	H	**3cb**	91.7	59
13	*o*-MeC_6H_4	Ph	H	Me	H	**3cc**	>99.9	75
14	*o*-MeC_6H_4	H	H	Me	H	**3cd**	–	40
15	*o*-MeC_6H_4	Me	Me	Me	H	**3ce**	–	14

[a] In all reactions were used 2 mmol of **2**, 4.2 mmol of **1**, Na_2CO_3/SiO_2 (1.5 mmol/g), PPA/SiO_2 (20 wt%) and 15 mL of PhCl.
[b] Isolated yield.



Scheme 2

When *m*-toluenethiol was used for this reaction, intramolecular cyclocondensation occurred at 2- and 4-positions in the benzene ring, and both 5-methylthiochromans (**3da**–**de**) and 7-methylthiochromans (**3′da**–**de**) were formed. Compounds **3** and **3′** could not be isolated from the mixture; therefore, these yields refer to a mixture of **3** and **3′** (Scheme 2).

Ishino et al. have reported stereoselective synthesis of thiochromans from arylthiols and α,β-unsaturated aldehydes in the presence of various protic and Lewis acids, and they found that *p*-toluene sulfonic acid (TsOH) was the most effective catalyst for a stereoselective synthesis of thiochromans. In the case of the reaction using TsOH, the formation of the *cis*-isomer of the thiochromans has priority over the *trans*-isomer. The method using supported reagents, however, gave preferentially the *trans*-isomer. The structure of the products and the ratio of *cis*- and *trans*-isomers were determined by ^{1}H NMR and H–H COSY. A proton signal at the 4-position in the *trans*-isomer showed a triplet (J = 2.9–3.2 Hz) whereas in the *cis*-isomer a doublet of doublet (J = 11.0–11.2, 5.1–5.4 Hz; see Figure 1) was observed. These results agreed with the Karplus rule. The protons at the 4- and 3-positions of the *trans*-isomer are located equatorial–axial and equatorial–equatorial on the thiopyran ring. The corresponding protons of the *cis*-isomer are located axial–equatorial and axial–axial. The structure of *trans*-**3aa** was also determined by X-ray crystal structure analysis and is shown in Figure 2. Preferential formation of the *trans*-isomer is due to intramolecular cyclocondensation occurring on the surface of PPA/SiO_2. There was no stereoselectivity observed when an intramolecular cyclocondensation was

carried out using PPA (see Figure 1), i.e. the reaction of benzenethiol (**1b**) and cinnamaldehyde (**2c**) in the presence of PPA gave a mixture of *cis*- and *trans*-**3bc**, in which the ratio of *cis*- and *trans*-isomer was 1.34:1.00. The mechanism of intramolecular cyclocondensation is now under investigation.

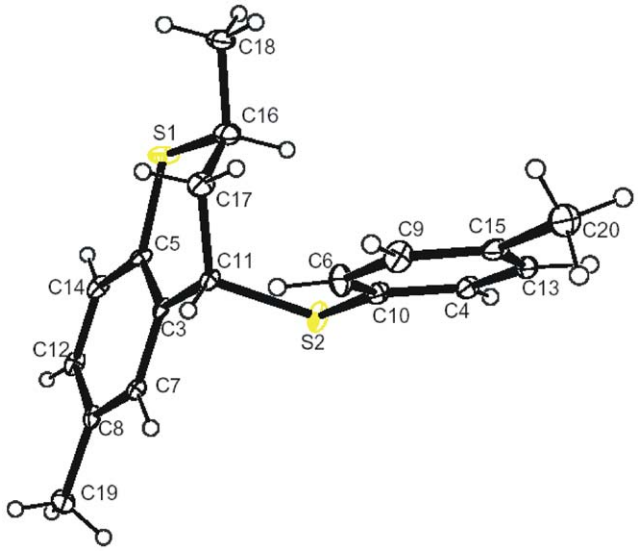


Figure 2 The molecular structure of *trans*-**3aa**

In conclusion, we developed a highly stereoselective synthesis of 2,4-disubstituted thiochromans from commercially available arylthiols and α,β-unsaturated aldehydes using the supported reagent system Na_2CO_3/SiO_2–PPA/SiO_2. It is particularly noteworthy that this method makes the neutralization of the reaction mixture and the *trans*-isomer of the products preferentially formed unnecessary.

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References and Notes

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(9) **Preparation of PPA/SiO_2.** PPA (4.0 g) and $CHCl_3$ (100 mL) were placed in the round-bottomed flask, and the mixture was stirred at 50 °C for 1 h. Then, SiO_2 [Wakogel C-200 (Wako Pure Chemical Ind. Ltd.), 16.0 g], which was dried in vacuo (10 mmHg) at 160 °C for 2 h, was added to the mixture, and the mixture was stirred for another 1 h. The $CHCl_3$ was removed with rotary evaporator and the resulting solid was dried in vacuo (10 mmHg) at r.t. for 3 h.
(10) **Preparation of Na_2CO_3/SiO_2.** Silica gel [Wakogel C-200 (Wako Pure Chemical Ind. LTD.), 16.82 g] was added to a solution of Na_2CO_3 (30 mmol, 3.18 g) in distilled H_2O (100 mL), and the mixture was stirred at r.t. for 0.5 h. Then, H_2O was removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 160 °C for 5 h.
(11) **Typical Procedure.** A mixture of arylthiols (4.20 mmol), α,β-unsaturated aldehydes (2.00 mmol), Na_2CO_3/SiO_2 (1.88 mmol, 1.25 g) and PPA/SiO_2 (20 wt%, 3.00 g) was stirred in PhCl (15 mL) at 80 °C for 4 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column chromatography eluted with hexane–EtOAc (300:1).
(12) Compound **3aa** (*trans*:*cis* = 1.0:0.1): yellow solid; mp 59.4–60.1 °C (hexane–EtOAc). Anal. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71. Found: C, 71.91; H, 6.79. HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}S_2$ [M^+]: 300.1006; found: 300.0999. IR (neat): 3015, 1489, 1479, 818, 780 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (0.27 H, d, *J* = 6.8 Hz), 1.31 (2.73 H, d, *J* = 6.8 Hz), 1.85 (0.91 H, ddd, *J* = 14.1, 11.7, 3.1 Hz), 1.99 (0.09 H, dt, *J* = 13.7, 10.7 Hz), 2.19 (0.91 H, dt, *J* = 14.1, 3.1 Hz), 2.22 (2.73 H, s), 2.27 (0.27 H, s), 2.32 (0.27 H, s), 2.35 (2.73 H, s), 2.50 (0.09 H, ddd, *J* = 13.7, 5.6, 2.9 Hz), 3.23–3.32 (0.09 H, m), 3.94–4.03 (0.91 H, m), 4.36 (0.09 H, dd, *J* = 10.7, 5.6 Hz), 4.47 (0.91 H, t, *J* = 3.1 Hz), 6.89–7.37 (7 H, m).
Compound **3ab** (*trans*:*cis* = 1.0:0.04): white solid; mp 77–78 °C (EtOH). Anal. Calcd for $C_{20}H_{24}S_2$: C, 73.12; H, 7.39. Found: C, 73.03; H, 7.36. HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}S_2$ [M^+]: 328.1319; found: 328.1320. IR (neat): 3019, 1493, 1479, 814, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (0.12 H, t, *J* = 7.3 Hz), 0.95 (2.88 H, t, *J* = 7.3 Hz), 1.40–1.50 (2.00 H, m), 1.55–1.62 (2.00 H, m), 1.85 (0.96 H, ddd, *J* = 14.1, 11.7, 3.2 Hz), 1.99 (0.04 H, dt, *J* = 13.7, 11.0 Hz), 2.23 (0.96 H, dt, *J* = 14.1, 3.2 Hz), 2.23 (2.88 H, s), 2.27 (0.12 H, s), 2.33 (0.12 H, s), 2.36 (2.88 H, s), 2.53 (0.04 H, ddd, *J* = 13.7, 5.6, 3.7 Hz), 3.18–3.25 (0.04 H, m), 3.88–3.95 (0.96 H, m), 4.35 (0.04 H, dd, *J* = 11.0, 5.6 Hz), 4.46 (0.96 H, t, *J* = 3.3 Hz), 6.89–7.38 (7 H, m).
Compound **3ac** (*trans*:*cis* = 1.0:0): white solid; mp 100–102 °C (acetone–hexane). Anal. Calcd for $C_{23}H_{22}S_2$: C, 76.24; H, 6.19. Found: C, 76.19; H, 6.12. HRMS (EI): *m*/*z* calcd for $C_{23}H_{22}S_2$ [M^+]: 362.1163; found: 362.1163. IR (neat): 3034, 1598, 1492, 1479, 807 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (3 H, s), 2.31 (3 H, s), 2.34–2.37 (2 H, m), 4.57 (1 H, t, *J* = 3.0 Hz), 5.10 (1 H, dd, *J* = 9.3, 5.4 Hz), 6.93–7.42 (12 H, m).
Compound **3ad**: oil. HRMS (EI): *m*/*z* calcd for $C_{17}H_{18}S_2$ [M^+]: 286.0850; found: 286.0851. IR (neat): 3016, 1597, 1491, 1482, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (1 H, ddt, *J* = 14.1, 12.4, 3.2 Hz), 2.22 (3 H, s), 2.22–2.29 (1 H, m), 2.32 (3 H, s), 2.69–2.75 (1 H, m), 3.68 (1 H, td, *J* = 12.4, 3.2 Hz), 4.44 (1 H, t, *J* = 3.2 Hz), 6.87–7.36 (7 H, m).
Compound **3ae**: oil. HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}S_2$ [M^+]: 314.1163; found: 314.1164. IR (neat): 3018, 1597, 1491, 1475, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (3 H, s), 1.38 (3 H, s), 2.14–2.25 (2 H, m), 2.30 (3 H, s), 2.33 (3 H, s), 4.42 (1 H, dd, *J* = 10.0, 6.4 Hz), 6.92–6.99 (2 H, m), 7.09 (2 H, d, *J* = 7.8 Hz), 7.26–7.29 (2 H, m), 7.65 (1 H, s).