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New Synthesis of Thioflavanones by the Regioselective Cyclization of 1-(2-Benzylthio)phenyl-3-phenyl-2-propen-1-ones with Hydrobromic Acid

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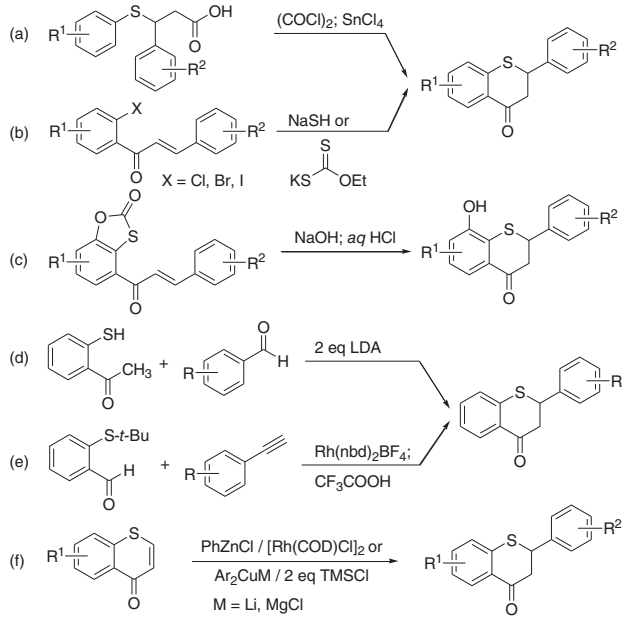
Thioflavanones have a skeleton of a thiochroman-4-one ring with aryl groups in the 2-position and unlike flavanones are not found naturally. Their pharmacological activities have recently been investigated in anticipation of improved bioavailability compared to flavanones. They inhibit the cellular proliferation of human breast cancer with weak cytotoxicity[1] and exhibit antioxidative activity[2] against nitric oxide (NO). They also have antileishmanial activity[3] against *Leishmania panamensis* and show better antifungal activity[4] against fungi, such as *Cryptococcus neoformans* and *Epidermophyton floccosum* than fluconazole.

Several methods for synthesizing thioflavanones have been described through the construction of thiochroman-4-one ring as a key step.[5] The reaction of thiophenols and cinnamic acids afforded 3-(phenylthio)-3-phenylpropanoic acids, which were converted to the corresponding acid chlorides with oxalyl chloride, followed by cyclization with $SnCl_4$ to give the thioflavanones (Scheme 1 (a)).[6] The treatment of 2′-halochalcones, which were prepared from 1-(2-halophenyl) ethanones and benzaldehydes using NaOH, with NaSH[7] or potassium ethyl xanthogenate/10 mol % $Cu(OAc)_2$[8] produced the corresponding 3-phenyl-1-(2-sulfanylphenyl)propenones *in situ*, followed by intramolecular 1,4-addition to afford the thioflavanones under heating conditions (Scheme 1 (b)). Alternatively, the reaction of oxathiolone-fused chalcones, which were prepared by the condensation of 4-acetyl-2-oxobenz[1,3]oxathiole with benzaldehydes using H_2SO_4, with NaOH afforded 8-hydroxythioflavanones in low-to-moderate yields by the deprotection and subsequent cyclization in refluxing CH_3OH (Scheme 1 (c)).[9]

The direct condensation of 2′-mercaptoacetophenone and benzaldehydes using 2 equiv. of lithium diisopropylamide (LDA) afforded thioflavanones through the attack of a sulfur atom to the corresponding chalcone intermediates (Scheme 1 (d)).[10] The combination of 2-(*tert*-butylthio) benzaldehyde and arylacetylenes using 5 mol % $Rh(nbd)_2BF_4$/dcpm afforded β'-(*tert*-butylthio)enone intermediates *in situ*, which underwent intramolecular *S*-conjugate addition to give thioflavanones after deprotection with an excess of CF_3COOH (Scheme 1 (e)).[11] Recently, thioflavanones were also synthesized by the 1,4-addition of phenylzinc chloride[12] or diarylcuprates[13] to thiochromones in the presence of $[Rh(COD)Cl]_2$ catalyst or 2 equiv. of TMSCl, respectively (Scheme 1 (e)).

Thus far, several methods for synthesizing thioflavanones have been reported, but some suffer from a lack of regioselectivity toward intramolecular cyclization, use of excess reagent, and multiple steps. Furthermore, there are few reports on the synthesis of thioflavanones by the cyclization of 2′-mercaptochalcones or *S*-protected thiochalcones and the scope of the reaction has not been fully investigated. Although the cyclization of thiolatechalcone intermediates, produced from *p*-methoxybenzylmercaptochalcones and $AgNO_3$ in refluxing EtOH, with *p*-toluenesulfonic acid gave thioflavanones, five steps are needed, resulting in low yields together with thioflavones as side products.[14] 2′-Mercaptochalcones were not readily isolated because the thiol group was oxidized easily to give the corresponding disulfide.[15] Initially, our attempt to prepare 2′-mercaptochalcone by the condensation of 2′-mercaptoacetophenone and benzaldehyde using KOH or $BF_3{\cdot}Et_2O$ were also unsuccessful. Thus, protection of the thiol group by avoiding oxidation was essential for the synthesis of thiochalcones. This article reports the efficient synthesis of thioflavanones by the regioselective cyclization of 1-(2-benzylthio)phenyl-3-phenyl-2-propen-1-ones with hydrobromic acid.

Initially, 1-(2-benzylthio)phenylethanone (**2**) was prepared in two steps: (1) The reaction of 2-mercaptobenzoic acid (**1**) and 3 equiv. of methyllithium in THF afforded 2′-mercaptoacetophenone in 81% yield. (2) The subsequent reaction of 2′-mercaptoacetophenone with benzyl chloride using KOH in THF afforded **2** in 92% yield. On the other hand, **2** was prepared conveniently by the treatment of **1** with 3 equiv. of methyllithium and successive addition of benzyl chloride in THF in a one-pot operation (Scheme 2). The sulfur atom of the resulting lithium thiophenolate intermediate was benzylated selectively after 4 h at room temperature. The mixture was quenched with a 1 N HCl solution and the THF evaporated off. After the usual acidic



Scheme 1. General method for synthesizing thioflavanones.

work-up and purification by recrystallization, **2** was obtained in 76% yield.

The condensation of **2** with arylaldehydes was carried out using 0.5 N KOH in THF. The reaction proceeded smoothly for 2–5 h between 0 °C and room temperature regardless of the type and position of substituents on the phenyl rings under the present conditions. The mixture was neutralized with a 0.5 N HCl solution and evaporated of THF. After the usual aqueous work-up and purification by recrystallization, **3a**-**l** were obtained as yellow solids in 77–90% yields.

To investigate the optimal conditions for the cyclization of **3**, the effect of acids and solvents for the reaction of 1-(2-benzylthio)phenyl-3-(4-methoxyphenyl)-2-propen-1-one (**3h**) was examined (Table 1). The cyclization of **3h** with HOAc solvent did not proceeded for 24 h at 65 °C and the starting material was recovered in 96% yield (entry 1). The cyclization of **3h** with CF_3COOH solvent and 5 equiv. of 70% $HClO_4$ in THF afforded 4′-methoxythioflavanone (**4 h**) in 90% and 45% yield, respectively, in 4 h/70 °C and 24 h/65 °C, respectively (entries 2–3). On the other hand, the cyclization of **3h** proceeded well with 1.5 equiv. of 48% HBr in CH_3CN to give **4h** in 93% yield after 1 h at 70 °C (entry 4). When HOAc, $ClCH_2CH_2Cl$, and DME were employed as solvents using 1.5 equiv. of 48% HBr, **4h** was obtained in 92, 84, and 0% yield, respectively, after 1.5, 24, and 24 h, respectively, at 70 °C (entries 5–7).

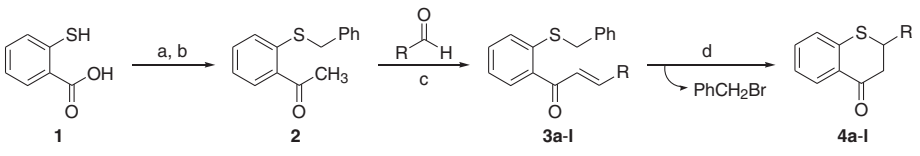
Thus, the 6-*endo* cyclization of **3** was accomplished successfully with 1.5 equiv. of 48% HBr in CH_3CN at 70 °C and the competitive 5-*exo* cyclized products were not observed. The reaction appeared to proceed through the debenzylation of the benzylthio group in **3** by HBr with the liberation of benzyl bromide to produce the corresponding 2′-mercaptochalcone intermediates, which underwent rapid 1,4-addition to give thioflavanones (**4**). The 6-*endo-digonal* cyclization was energetically favorable compared to 5-*exo-digonal* cyclization as Baldwin's rule.[16] This synthetic method of thioflavanones via *S*-protected chalcone intermediates showed the advantage of the short steps, the exclusive 6-*endo* cyclization, and the high yields compared with those using oxathiolone-fused chalcones[9] and *p*-methoxybenzylmercaptochalcones.[14] The characteristic ^1H NMR spectra of the synthesized thioflavanones appeared as a doublet of doublets for the C_2 proton signals in the range of 4.67–5.22 ppm and two doublets of doublets for two C_3 protons signals in the range of 3.27—3.36 ppm and 3.13–3.26 ppm, respectively.

As presented in Table 2, various thioflavanone derivatives were synthesized from 1-(2-benzylthio)phenyl-3-phenyl-2-propen-1-ones and 48% HBr in high overall yields (48–61%). The selective 6-*endo* cyclization of **3a**-**l** proceeded well regardless of the types and the positions of electron-donating (**4b**, **4c**, **4g**–**4j**) and electron-withdrawing (**4d**-**4f**) substituents on the 2-substituted phenyl rings to give the corresponding thioflavanones under the described conditions. Furthermore, the reaction of **3** containing the heteroaromatic groups, 2-furyl (**3k**) and 2-thienyl (**3l**), proceeded equally well to give the corresponding 2,3-dihydro-2-(2-heteroaryl)-4*H*-thiopyran-4-ones in 90% and 88% yield, respectively.

In conclusion, a regioselective method was developed for the synthesis of thioflavanones from 1-(2-benzylthio)phenyl-3-phenyl-2-propen-1-ones using 48% HBr in CH_3CN in high yields.

Experimental

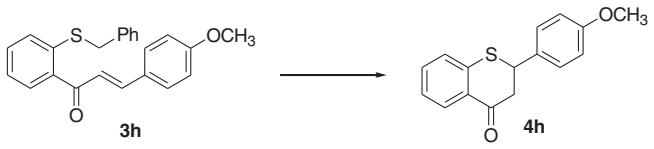
Preparation of 1-(2-Benzylthio)phenylethanone (2). Methyllithium (1.5 M in Et_2O, 11.0 mL, 16.5 mmol) was



R = C_6H_5 (**a**); 2-CH_3O-C_6H_4 (**b**); 3-HO-C_6H_4 (**c**); 3-O_2N-C_6H_4 (**d**); 4-F-C_6H_4 (**e**); 4-Cl-C_6H_4 (**f**); 4-CH_3-C_6H_4 (**g**); 4-CH_3O-C_6H_4 (**h**); 3,4-$(CH_3O)_2$-C_6H_3 (**i**); 3,4,5-$(CH_3O)_3$-C_6H_2 (**j**); 2-furyl (**k**); 2-thienyl (**l**)

Scheme 2. Reagents and conditions: (a) 3 equiv. CH_3Li, THF, 0 °C, 15 min; (b) $PhCH_2Cl$, rt, 4 h in one-pot; 1 N HCl; (c) 0.5 N KOH, THF, 0 °C-rt, 2–5 h; (d) 1.5 equiv. 48% HBr, CH_3CN, 70 °C, 1–4 h.

Table 1. Effect of acids and solvents for the cyclization of 1-(2-benzylthio)phenyl-3-(4-methoxyphenyl)-2-propen-1-one (**3h**)



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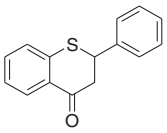
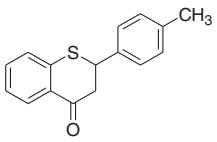
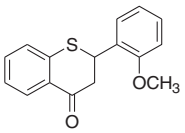
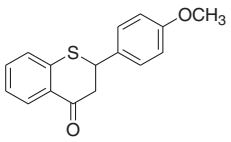
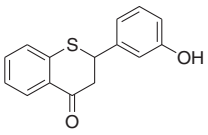
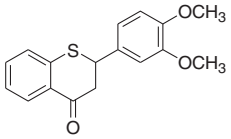
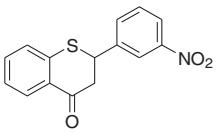
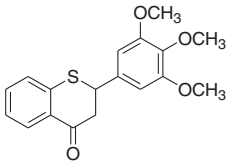
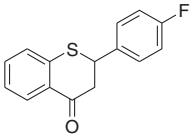
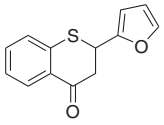
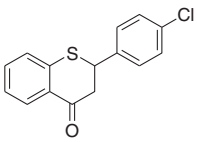
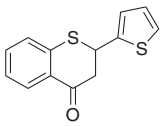
Entry	Acids	Solvents	Temp (°C); time (h)	Yields of 4h, %[a]
1	HOAc	-	65; 24	0 (96)
2	CF_3COOH	-	70; 4	90
3	70% $HClO_4$[b]	THF	65; 24	45
4	48% HBr[c]	CH_3CN	70; 1	93
5	48% HBr[c]	HOAc	70; 1.5	92
6	48% HBr[c]	$ClCH_2CH_2Cl$	70; 24	84
7	48% HBr[c]	DME	70; 24	0

[a] The number in parenthesis indicates the recovery yield of **3h**.
[b] 5 equiv. was used.
[c] 1.5 equiv. was used.

Table 2. Synthesis of **3** and thioflavanones **4**.[a]

Entry	Thioflavanones	Yields, %[b] **3** **4**	Entry	Thioflavanones	Yields, %[b] **3** **4**
a		82 87 (54)	**g**		88 90 (60)
b		87 93 (61)	**h**		83 93 (59)
c		77[c] 82 (48)	**i**		85 91 (59)
d		84 83 (53)	**j**		88 82 (55)
e		86 81 (53)	**k**		86 90 (59)
f		90 83 (57)	**l**		87 88 (58)

[a] The conversion of **3** to **4** was carried out using 1.5 equiv. of 48% HBr in CH_3CN at 70 °C.
[b] The numbers in parentheses indicate the overall yields from 2-mercaptobenzoic acid **1**.
[c] 2 equiv. of 0.5 N KOH were used.

added slowly to a solution of 2-mercaptobenzoic acid (**1**, 771 mg, 5.0 mmol) in THF (20 mL) under argon atmosphere at 0 °C. After stirring for 15 min, benzyl chloride (633 μL, 5.5 mmol) was added to the resulting yellow lithiophenylthiolate solution and stirred for 4 h at room temperature. The reaction mixture was quenched with a 1 N HCl solution (5 mL) and THF was evaporated. The mixture was poured into a 0.1 N HCl solution (50 mL) and extracted with methylene chloride (3 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was recrystallized twice in 10% EtOAc/*n*-hexane to give **2** (921 mg, 76%). mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 1H), 7.36–7.42 (m, 4H), 7.29–7.34 (m, 2H), 7.24–7.29 (m, 1H), 7.17–7.23 (m, 1H), 4.13 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 140.8, 136.3, 135.5, 132.1, 130.8, 129.1, 128.6, 127.3, 126.7, 124.2, 37.8, 28.5; FTIR (KBr) 1670 (C═O) cm^{-1}.

Preparation of 1-(2-Benzylthio)phenyl-3-(4-methoxyphe-yl)-2-propen-1-one (3h). Potassium hydroxide (0.5 N in CH_3OH, 6.0 mL, 3.0 mmol) was added to a mixture solution of **2** (727 mg, 3.0 mmol) and 4-methoxybenzaldehyde (409 mg, 3.0 mmol) in THF (10 mL) at 0 °C. Stirring was continued for 5 h between 0 °C and room temperature and the mixture was then quenched with a 0.5 N HCl solution (6 mL). After evaporating the solvent, the mixture was poured into a 0.1 N HCl solution (40 mL), extracted with methylene chloride (3 × 20 mL), and washed with a saturated $NaHCO_3$ solution (40 mL). The concentrated residue was recrystallized twice in 50% EtOAc/*n*-hexane to give **3h** (898 mg, 83%). mp 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.34–7.44 (m, 3H), 7.19–7.32 (m, 6H), 7.09 (d, J = 15.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 4.11 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 161.7, 145.5, 140.2, 136.8 (overlapped), 130.8, 130.3, 129.8, 129.0, 128.9, 128.5, 127.4, 127.2, 125.6, 123.4, 114.4, 55.4, 39.2; FTIR (KBr) 1635 (C═O) cm^{-1}.

Preparation of 4′-Methoxythioflavanone (4 h). Hydrobromic acid (48 wt % in H_2O, 340 μL, 3.0 mmol) was added to a solution of **3h** (721 mg, 2.0 mmol) in CH_3CN (8 mL) and stirred for 1 h at 70 °C. Acetonitrile was then evaporated under reduced pressure. The mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with methylene chloride (3 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Benzyl bromide was evaporated further under high vacuum and the residue was then recrystallized twice in 10% EtOAc/*n*-hexane to give **4h** (502 mg, 93%) as a pale yellow solid. Physical and spectral data for the thioflavanone compounds associated with this article can be found in the Supporting Information.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

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