A Novel Synthesis of Heterocyclic Analogues of Thioflavanones from Haloheteroaromatic Carboxylic Acids

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Thioflavanones (2-phenylthiochroman-4-ones), the thio analogues of flavanones, are an interesting class of heterocycles because their biological activities sometimes can be improved. We recently investigated the anticancer effects of thioflavanone in MCF-7 human breast cancer cell lines and found that it inhibited cellular proliferation by inducing apoptosis with weak cytotoxicity.

The 3-cinnamylidene derivatives of thioflavanones showed antiproliferative effects on mouse lymphoma cells, and the 3-chloromethylene derivatives of thiochroman-4-ones showed antifungal activities.

Thiochroman-4-ones have been generally synthesized by the Friedel-Crafts acylation of 3-arylthiopropanoic acids, which are prepared by adding thiophenols to α,β-unsaturated esters or substituting 3-bromo (mesyl) esters with thiophenols and subsequent hydrolysis, with H₂SO₄ or polyphosphoric acid in moderate yields. The cyclization of 3-arylthiopropanoic acids proceeded by a catalytic amount of Lewis acid, such as Bi(NTf₂)₃ or Yb(OTf)₃, at 200 °C.

The direct cyclocondensation of thiophenols and 3-methyl-2-butenoic acid with methanesulfonic acid resulted in thiochroman-4-ones, with the corresponding disulfides and enol thioethers obtained as minor products.

Another thioflavanone synthesis involved intramolecular cyclization of 2′-mercaptochalcones, which are prepared by the base catalyzed condensation of 2-benzthioacetophenones and benzaldehydes followed by subsequent debenzylation, with p-toluenesulfonic acid or phosphomolybdic acid supported on silica (PMA-SiO₂). The cyclization of S-benzyl protected α-sulfinyl chalcones followed by debenzylation with formic acid proceeds smoothly to give 3-sulfinylthioflavanones. These compounds undergo sulfinyl group elimination to form thioflavones in refluxing benzene.

Despite potential in bioisosterism of thioflavanones, only a few synthetic methods are reported for heterocyclic analogues. As an extension of our research on thioflavonoids, we describe the novel synthesis of heterocyclic analogues of thioflavanones from haloheteroaromatic carboxylic acids as potential drug candidates.

Initial attempts to prepare 1-(haloheteroaryl)ethanones (3) directly by treating haloheteroaromatic acids (1) with 2 equiv of methyllithium were fruitless. Therefore, 3 were synthesized via 2-pyridyl haloheteroaroates (2), which were readily prepared from 1 using di-2-pyridyl carbonate (2-DPC) according to previously developed method (2a: 83%, 2b: 90%, 2c: 87%, 2d: 87%, Scheme 1). The synthesis of 3 was successfully accomplished by nucleophilic acyl substitution of 2 with methyllithium. The addition of methyllithium chloride to a solution of 2 in THF at 0 °C led to the formation of precipitates, which were hydrolyzed with saturated NH₄Cl solution to give 3 (3a:

Scheme 1
Haloheteroaryl chalcones (4) were synthesized by condensation between 3 and (hetero)arylaldehydes using KOH. The treatment of a solution of 3 and (hetero)arylaldehydes in EtOH with 0.5 N KOH afforded corresponding β-hydroxyketones which then underwent dehydration to give 4. After completing the reaction, the resulting yellow solution containing white precipitates was quenched with 0.5 N HCl and separated by aqueous workup. Purification of the residue by silica gel column chromatography or recrystallization afforded 4 in 68-89% yields.

The cyclization of 4 was carried out by one-pot sequence of a 1,4-addition of sodium hydrosulfide followed by intramolecular substitution of halides. The addition of 4 to a suspended solution of sodium hydrosulfide in EtOH at room temperature prompted 1,4-addition of hydrosulfide anion to result in sodium thiolate adducts (5). These intermediates underwent intramolecular nucleophilic aromatic substitution at reflux for 1.5-4 h to give the heterocyclic analogues of thioflavanones (6) by eliminating sodium halides. After completing the reaction, the resulting light yellow solution containing precipitates was treated with H₂O and separated by aqueous workup. The residue was purified by silica gel column chromatography or recrystallization in 10% EtOAc/n-hexane to give 6 in 87-93% yields. The characteristic ¹H NMR absorptions of 6 appeared as a doublet of doublets for the C₂ proton signals from δ 4.74 to 5.35 and two doublet of doubles for two C₃ protons signals from δ 3.07 to 3.43.

As shown in Table 1, various heterocyclic thioflavanone analogues were synthesized with overall high yields (50-62%) from readily available starting material 1. The reaction proceeded equally well with 2-bromothiophene (6bf, 6bl, 6bn) and 3-chlorothiophene groups (6ag, 6am), regardless of the position of the 2-bromo or 3-chloro group in thiophenecarboxylic acids. The reaction also proceeded well for the electron-withdrawing substituents, such as chloro (6ag, 6bf) and nitro groups (6ci), and electron-donating substituents, such as methoxy (6bl, 6ck) and methyl groups (6dj), of 2-substituted phenyl rings. Without protection of hydroxyl group, 4ch was also cyclized to afford 6ch. Furthermore, the present method was applicable for synthesizing 6 containing a heteroaromatic ring, such as 2-furyl (6am) or 2-thienyl (6bn), in place of phenyl group.

In conclusion, the present method provides (i) novel synthesis of heterocyclic thioflavanone analogues 6 from starting material 1, (ii) a rapid and versatile reaction, and (iii) overall high yields.

### Experimental Section

**General Procedure for Synthesizing 1-(2-Chloropyridin-3-yl)ethanone (3c).** Methylmagnesium chloride (0.5 M in THF, 8.0 mL, 4.0 mmol) was added to a solution of 2-pyridyl 2-chloropyridine-3-carboxylate (2c, 939 mg, 4.0...
mmol) in THF (12 mL) at 0 °C under argon atmosphere. After stirring for 0.5 h, the mixture was quenched with saturated NH₄Cl solution (5 mL) and THF was evaporated in vacuo. The mixture was poured into saturated NH₄Cl solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo.


General Procedure for Synthesizing 1-(2-Chloropyridin-3-yl)-3-(4-methoxyphenyl)-2-propen-1-one (4ck). A 0.5 N KOH solution (0.5 N in CH₂OH, 6.0 mL, 3.0 mmol) was added to a mixture of 3c (467 mg, 3.0 mmol) and 4-methoxyphenyl)-4-one (3.87 (s, 6H), 3.86 (s, 3H), 3.23 (dd, J = 5.4 Hz, 1H); 13C NMR (75 MHz, CDCl₃) δ 134.9, 133.6, 130.3, 129.8, 128.2, 127.5, 126.1, 122.5, 104.5, 60.9, 56.2, 50.2, 45.8; FT-IR (film) 1663 (C=O) cm⁻¹; Ms m/z (%) 282 (M⁺/2, 43), 280 (M⁺, 100), 169 (72), 142 (98).

5.6-Dihydro-5-(4-chlorophenyl)-7H-thieno[3,2-b]thiopyran-4-one (6ag): mp 152–156 °C; 1H NMR (300 MHz, CDCl₃) δ 7.70 (d, J = 5.1 Hz, 1H), 7.35–7.39 (m, 4H), 6.95 (d, J = 5.1 Hz, 1H), 4.88 (dd, J = 13.1 Hz, J = 3.2 Hz, 1H), 3.27 (dd, J = 16.6 Hz, J = 13.1 Hz, 1H), 3.07 (dd, J = 16.6 Hz, J = 3.2 Hz, 1H); 13C NMR (75 MHz, CDCl₃) δ 187.5, 144.9, 136.5, 135.1, 134.5, 131.7, 129.2, 128.9, 126.8, 47.6, 45.5; FT-IR (KBr) 1652 (C=O) cm⁻¹; Ms m/z (%) 282 (M⁺/2, 43), 280 (M⁺, 100), 169 (72), 142 (98).

General Procedure for Synthesizing 2,3-Dihydro-2-(4-methoxyphenyl)-4H-thiopyran[2,3-b]pyridin-4-one (6ck). A solution of 4ck (547 mg, 2.0 mmol) in EtOH (15 mL) was added to a suspended solution of hydroxylsulfide hydrate (60%, 224 mg, 2.4 mmol) in EtOH (10 mL) at room temperature. The solution was stirred for 0.5 h at room temperature to give tan solution and then refluxed for 3 h more. After evaporating EtOH, the mixture was poured into saturated NH₄Cl solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo.

(dd, $J_1 = 16.3$ Hz, $J_2 = 12.7$ Hz, 1H), 3.22 (dd, $J_1 = 16.3$ Hz, $J_2 = 3.3$ Hz, 1H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.0, 164.1, 153.9, 137.8, 136.6, 129.1, 128.7, 125.7, 125.9, 120.3, 45.8, 44.1; FT-IR (film) 1682 (C=O) cm$^{-1}$; Ms m/z (%) 241 (M$^+$, 100), 164 (21), 137 (26), 104 (32).

2.3-Dihydro-2-(3-hydroxyphenyl)-4H-thiopyran[2,3-b]pyridin-4-one (6cb): mp 182-183 °C; $^1$H NMR (300 MHz, CDCl$_3$/DMSO-d$_6$ = 3/1) $\delta$ 9.29 (s, 1H), 8.55 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.8$ Hz, 1H), 8.29 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 1H), 7.15-7.23 (m, 2H), 6.85-6.91 (m, 2H), 6.79 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.2$ Hz, 1H), 4.77 (dd, $J_1 = 12.5$ Hz, $J_2 = 3.1$ Hz, 1H), 3.31 (dd, $J_1 = 16.3$ Hz, $J_2 = 12.5$ Hz, 1H), 3.15 (dd, $J_1 = 16.3$ Hz, $J_2 = 3.1$ Hz, 1H); $^1$C NMR (75 MHz, CDCl$_3$/DMSO-d$_6$ = 3/1) $\delta$ 198.4, 168.5, 162.7, 158.5, 144.1, 141.1, 134.8, 131.6, 125.2, 122.9, 120.5, 119.3, 50.4, 48.4; FT-IR (KBr) 3420 (OH), 1653 (C=O) cm$^{-1}$; Ms m/z (%) 257 (M$^+$, 100), 164 (22), 138 (26), 120 (49).

2.3-Dihydro-2-(3-nitrophenyl)-4H-thiopyran[2,3-b]pyridin-4-one (6ci): mp 154-155 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.60 (dd, $J_1 = 4.7$ Hz, $J_2 = 1.9$ Hz, 1H), 8.34-8.38 (m, 2H), 8.24 (d, $J = 8.1$ Hz, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.21 (dd, $J_1 = 7.9$ Hz, $J_2 = 4.7$ Hz, 1H), 4.88 (dd, $J_1 = 11.9$ Hz, $J_2 = 3.5$ Hz, 1H), 3.39 (dd, $J_1 = 16.2$ Hz, $J_2 = 11.9$ Hz, 1H), 3.28 (dd, $J_1 = 16.2$ Hz, $J_2 = 3.6$ Hz, 1H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 192.9, 162.9, 154.2, 148.6, 140.0, 136.7, 133.6, 130.3, 126.9, 123.7, 122.7, 120.7, 45.2, 43.2; FT-IR (KBr) 1682 (C=O) cm$^{-1}$; Ms m/z (%) 286 (M$^+$, 100), 164 (18), 137 (93), 109 (35).

2.3-Dihydro-2-(4-methylphenyl)-4H-thiopyran[2,3-b]quinolin-4-one (6dj): mp 134-135 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.86 (s, 1H), 7.94 (d, $J = 8.5$ Hz, 1H), 7.87 (d, $J = 8.1$ Hz, 1H), 7.75-7.80 (m, 1H), 7.47-7.52 (m, 1H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.20 (d, $J = 7.7$ Hz, 2H), 4.82 (dd, $J_1 = 12.0$ Hz, $J_2 = 2.9$ Hz, 1H), 3.43 (dd, $J_1 = 16.3$ Hz, $J_2 = 12.0$ Hz, 1H), 3.31 (dd, $J_1 = 16.3$ Hz, $J_2 = 3.0$ Hz, 1H), 2.36 (s, 3H); $^1$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.4, 161.6, 150.0, 138.5 (overlapped), 135.0, 133.1, 129.9, 129.8, 128.0, 127.4, 126.5, 125.5, 125.2, 46.7, 43.5, 21.2; FT-IR (KBr) 1686 (C=O) cm$^{-1}$; Ms m/z (%) 305 (M$^+$, 100), 213 (24), 118 (31), 105 (35).

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References