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A rapid entry into thioflavanones via conjugate additions of diarylcuprates to thiochromones

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ABSTRACT

Thiochromone undergo conjugate addition reactions with arylcuprates to afford 2-substituted thioflavanones, providing an efficient synthetic approach to privileged sulfur-containing structural motifs and valuable precursor for many pharmaceuticals. Excellent yields of substituted thioflavanones are achieved with lithium diarylcuprates, lithium arylcyanocuprates and Grignard reagents with copper catalysis. This method provides a rapid entry to a variety of thioflavanones in excellent yields (up to 92%). The use of commercially available or easily prepared organometallic reagents will expedite the synthesis of a large library of thioflavanones for further synthetic applications and biological studies.

1. Introduction

Sulfur-containing heterocycles/subunits are widely present in many pharmaceutical active molecules and bioactive natural products.[1] There has been increasing interest in the development of efficient synthetic approaches to sulfur-containing compounds due to their widespread applications in medicinal chemistry, biology, food chemistry and material science.[1,2] Compared to the oxygen-containing analog, the sulfur-containing compounds are much less studied area. For example, flavonoids, especially flavanones are important class of oxygen-containing heterocycles and are widely present in numerous pharmaceutical active molecules as well as bioactive natural products. Flavonoids and substituted flavonoids have been well studied and found to exhibit many biological activities including antioxidant, antitumor, and anti-inflammatory properties.[3] Thioflavonoids (Scheme 1), the sulfur analogues of flavonoids, also display many biological activities such as antimicrobial, antioxidant, inhibiting nitric oxide production, and antifungal.[4] For example, thioflavanones have been reported to significantly inhibit cellular proliferation with weak cytotoxicity and induce apoptosis in human breast cancer cells.[5,6] It has been reported that modification of the functional groups on aromatic ring of thioflavanones resulted in the significantly increased antioxidant activities and inhibitory activities against nitric oxide production.[7] Known as an important class of heterocycles,[1c,d] thioflavanones are vital precursors of bioactive thiochhroman-4-one 1,1-dioxanes as well as benzothiazepins.[4c,d,8] Unlike flavanones, which are abundant in citrus fruits and widely present in many plants in nature, thiofavanones are not found in nature. Thus, development of efficient synthetic routes to structurally diverse thioflavanones is critical in studying and improving their bioavailability and bioactivity.

Although many synthetic approaches to thiochroman-4-ones, thioflavone and thiochromones have been reported in literature,[9–11] reports on efficient synthesis of thioflavanones are scarce. Previous synthetic approaches to thioflavanones generally revolve around four strategic approaches: (A) hydrogenation of thiochromones[12]; (B) Friedel-Crafts acylation of thiopropanoic acid[13]; (C) intramolecular thio-Michael addition[14]; and more recently, (D) Rh-catalyzed conjugate addition to thiochromones.[15] A rhodium-catalyzed alkyne hydroacylation/thio-conjugate addition sequence in synthesis of thio-4-chromanones including thioflavanones has also been reported recently.[16] Among these approaches, methods A

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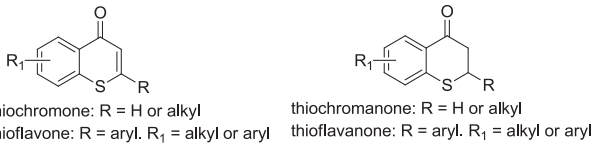


Scheme 1. Structures of Thiochromone, Thiochromanone, Thioflavone, and Thioflavanones.

and B are not particularly suitable for synthesis of 2-aryl substituted thioflavanones. To the best of our knowledge, conjugate addition of organocuprates to thiochromones has not been reported despite the fact that conjugate addition reaction of organocuprates to Michael-acceptors is one of the most reliable carbon carbon bond forming strategies.[17] We now report the first conjugate addition of organocuprates to thiochromones **1** to afford 1,4-adducts thioflavanones **2** in excellent yields (Fig. 1).

2. Results and discussions

We commenced our study with PhLi, copper (I) salt and thiochromone to optimize the reaction condition. When 0.3 equivalent of CuI was added as catalyst to effect 1,4-conjugate addition of PhLi to thiochromone **3A** in THF, no 1,4-adduct **4Aa** was formed (Table 1, entry 1, 0%). Cyanocuprate (i.e., PhCuCNLi) also fail to add to thiochromone with recovery of unreacted thiochromone (Table 1, entry 2, 0%) under this reaction condition. Under similar reaction condition, more reactive Gilman reagents (i.e., Ph_2CuLi) offered only trace amount of 1,4-adduct **4Aa** (Table 1, entry 3). These results demonstrated that thiochromone are very sluggish towards the addition of organocopper reagents.

Trimethylsilyl chloride (TMSCl) has been reported to accelerate 1,4-conjugate additions of both stoichiometric cuprates and catalytic amount of copper (I) salts.[18] It is generally thought that TMSCl stabilized the Cu π-complex intermediate by converting it to a reactive tetravalent copper species that is capable of a rapid reductive elimination to form 1,4-adduct.[18g] We decided to investigate the effect of TMSCl on this reaction. With the addition of TMSCl, the yield of desired 1,4-adduct **4Aa** can be increased to 70% (Table 1, entry 4). A slightly higher yields can be achieved when the amount of CuI was increased to 1.5 equivalent (Table 1, entry 7). Similarly, CuCN also promoted conjugate addition of PhLi to thiochromone **3A** in the presence of TMSCl (Table 1, entries 8–10). The chemical yield of 1,4-adduct **4Aa** can be improved to 78% with 0.3 equiv of CuCN and addition of LiCl as additive in the present of TMSCl (Table 1, entry 11). With the addition of TMSCl, lithium cyanocuprate reagent underwent smooth conjugate addition to thichromone **3A** with 82% yield (Table 1, entry 12). Lithium diphenylcuprate gave the highest yield of 1,4-adduct **4Aa** at 90% (Table 1, entry 13) and it is consistent with the reactivity pattern that Gilman reagents (Ph_2CuLi) are generally more reactive than the cyanocuprate reagents (PhCuCNLi). Comparable chemical yields of **4Aa** can be achieved when the organocuprates are prepared from the Grignard reagent PhMgBr (Table 1, entries 14, 15).

The control experiment showed that PhLi failed to afford any 1,4-adduct **4Aa** without any copper(I) salt in the presence of 2.0 equiv TMSCl in THF. With $Cu(OTf)_2$ added (1.0 equiv), only trace amount of 1,4-adduct **4Aa** were attained (3%) as over 90% starting material **3A** was recovered.

With the optimal reaction condition in hand, we next examined the scope of diarylcuprates (i.e., Ar_2CuLi or $Ar_2CuMgBr$) conjugate addition to thiochromone **3A** (Table 2, entries 1–14). In general, a

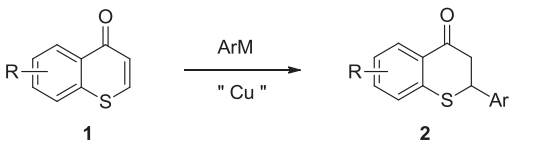
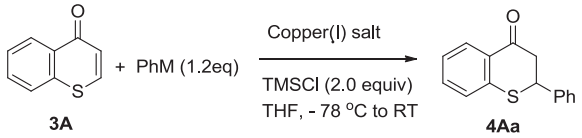


Fig. 1. Conjugate addition of organocopper reagents to thiochromones.

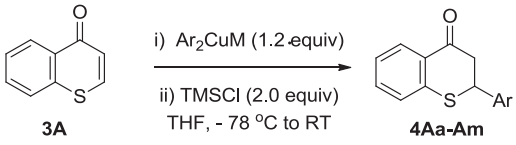
Table 1
Optimization of 1,4-conjugate addition of organocuprates to Thiochromone.



Entries[a, b]	PhM	Copper (I) salt/reagent	TMSCl (equiv)	Yield[c] (%)
1	PhLi	CuI (0.3 equiv)	0	0
2	PhLi	PhCuCNLi	0	0
3	PhLi	Ph_2CuLi	0	trace
4	PhLi	CuI (0.3 equiv)	2.0	70
5	PhLi	CuI (0.3 equiv)	2.0	75[d]
6	PhLi	CuI (0.3 equiv)	2.0	73[e]
7	PhLi	CuI (1.5 equiv)	2.0	77[d]
8	PhLi	CuCN (0.3 equiv)	2.0	69
9	PhLi	CuCN (0.3 equiv)	2.0	72[d]
10	PhLi	CuCN (1.5 equiv)	2.0	71
11	PhLi	CuCN·2LiCl (0.3 equiv)	2.0	78
12	PhLi	PhCuCNLi	2.0	82
13	PhLi	Ph_2CuLi	2.0	90
14	PhMgBr	PhCuCNMgBr	2.0	80
15	PhMgBr	$Ph_2CuMgBr$	2.0	88

[a] Reagents were prepared by adding PhLi or PhMgBr to CuCN or CuI. All the reactions were performed in the presence of 2.0 equiv of TMSCl unless noted otherwise.
[b] PhLi and PhMgBr are commercially available.
[c] Yields are based on isolated products by column chromatography.
[d] Organocopper reagents were prepared at 0 °C, then cooled to −78 °C.
[e] The reaction was run at 0 °C.

Table 2
Reactions of diarylcuprates with Thiochromone.



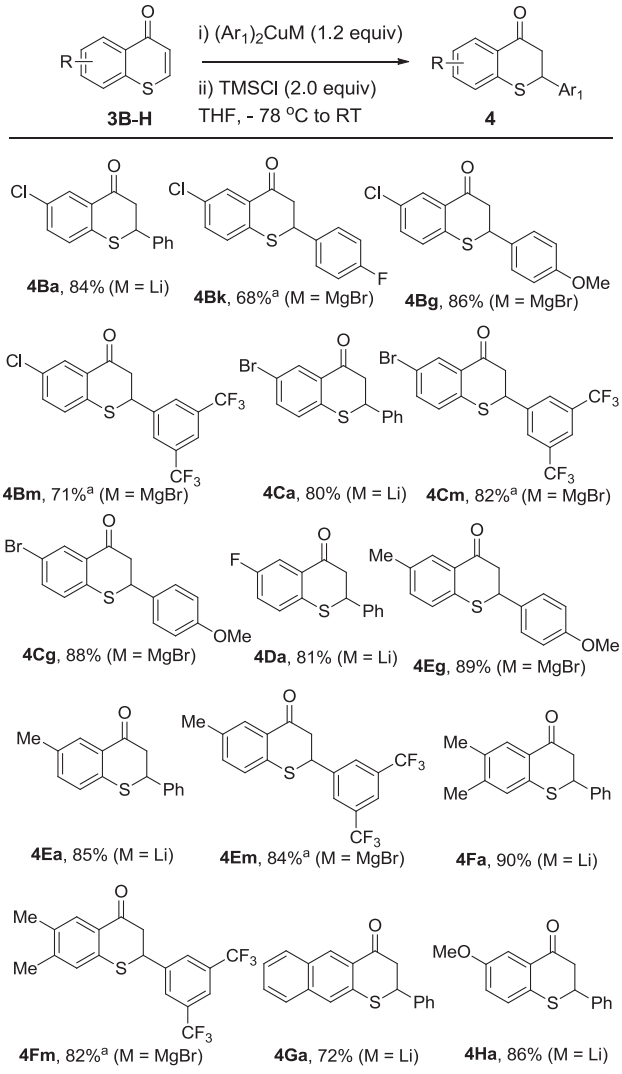
Entries[a,b]	Ar	M	equiv	Product	Yield[c]
1	C_6H_5	Li	1.2	**4Aa**	90%
2	2-MeC_6H_4	Li	1.2	**4Ab**	81%
3	4-MeC_6H_4	MgBr	1.2	**4Ac**	88%
4	4-PhC_6H_4	MgBr	1.2	**4Ad**	91%
5	2-Naphthyl	MgBr	1.2	**4Ae**	86%
6	3,5-$Me_2C_6H_3$	MgBr	1.2	**4Af**	89%
7	4-MeOC_6H_4	MgBr	1.2	**4Ag**	92%
8	2-MeOC_6H_4	MgBr	1.2	**4Ah**	83%
9	3-Me-4-MeOC_6H_3	MgBr	1.2	**4Ai**	86%
10	3-MeOC_6H_4	MgBr	1.2	**4Aj**	87%
11	4-FC_6H_4	MgBr	1.2	**4Ak**	65%
12	4-$CF_3C_6H_4$	MgBr	1.2	**4Al**	69%
13	3,5-$(CF_3)_2C_6H_3$	MgBr	1.2	**4Am**	76%
14	3,5-$(CF_3)_2C_6H_3$	MgBr	2.4	**4Am**	88%

[a] All reactions were performed using 1.2 equiv of Ar_2CuM in the presence of 2.0 equiv of TMSCl unless noted otherwise.
[b] ArLi or ArMgBr are either commercially available or prepared from corresponding ArBr and used in situ as a THF solution.
[c] Yields are based on isolated products by column chromatography.

broad range of diarylcuprates underwent smooth conjugate addition to thiochromone **3A** to afford 1,4-adducts **4Aa**-**Am** with good to excellent chemical yields (Table 2).

Simple diarylcuprates such as diphenylcuprates and dinaphthylcuprates add to **3A** with excellent chemical yields (Table 2, entries 1, 5). The diarylcuprates with electron donating substituents on aromatic ring usually add to thiochromone smoothly (Table 2, entries 3, 4, 6, 7, 9, 10). The ortho-substituted arylreagents gave lower yields presumably due to steric hindrance (entries 2, 8). The diarylcuprate reagents with strong electron withdrawing groups such as fluoro, trifluoromethyl, bistrifluoromethyl groups on aryl ring also underwent conjugate addition but with lower chemical yields (entries 11–13). The yield of 1,4-adduct can be significantly improved when large excess of diarylcuprates with strong electron withdrawing groups on aryl ring was used. For example, with bistrifluoromethyl groups on phenyl ring, when 2.4 equivalent of di(3,5-bistryfluoromethyl)phenylcuprate was used and the yield of 1,4-adduct **4Am** can be improved to 88% (Table 2, entry 14).

To explore the scope of thiochromones, a number of substituted thiochromones **3B**-**H** were also investigated. Diarylcuprates with both electron-withdrawing and electron-donating substituents on aryl ring were investigated (Scheme 2). Diphenylcuprates (i.e., Ph_2CuLi) add to substituted thiochromones **3B**-**H** smoothly to afford 1,4-adducts **4** with good yields (72–90%). With an electron-donating group on the aromatic ring (4-MeO-), $(4\text{-MeOPh})_2CuMgBr$ is more reactive than Ph_2CuLi or $Ph_2CuMgBr$ with all the substituted thiochromones investigated (Scheme 2, 86–89%). Diarylcuprates with strong electron-donating groups on aromatic ring are generally less reactive and gave slightly lower yields (Scheme 2, 68–82%).



1. All the reactions were performed using 1.2 equiv of $(Ar_1)_2CuM$ in the presence of 2.0 equiv of TMSCl unless noted otherwise. 2. Ar_1Li or Ar_1MgBr were either commercially available or prepared from corresponing Ar_1Br and used in situ as THF solution. 3.Yields are based on isolated products by column chromatography. a. Reactions were performed using 2.4 equiv of $(Ar_1)_2CuM$.

Scheme 2. Reactions of Diarylcuprates with Substitututed Thiochromones.

3. Conclusion

In conclusion, we have successfully developed the first conjugate addition of diarylcuprates to thiochromone and substituted thiochromones in the presence of chlorotrimethylsilane (TMSCl). TMSCl showed remarkable accelerating effects on 1,4-conjugate addition of diarylcuprates to thiochromones. This reaction is compatible with a broad scope of diarylcuprates with both electron-donating and electron-withdrawing substituents on aromatic rings to afford a variety of thioflavanones with excellent chemical yields. Further studies on synthetic applications using these thioflavanones as key intermediates are ongoing in our lab.

4. Experimental section

4.1. General methods

The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a BRUKER Ascend™ 400 NMR spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C and 376 MHz for ^{19}F. Some samples were recorded on a BRUKER 300 NMR spectrometer, operating at 300 MHz for ^1H and 75 MHz for ^{13}C and 282 MHz for ^{19}F. Samples for NMR spectra were dissolved in deuterated chloroform (with TMS). Infrared (IR) spectra were recorded on a Nicolet iS10 FT-IR spectrometer as neat samples (thin films). Analytical thin layer chromatography (TLC) was performed on silica gel plates, 60 μ mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid and/or $KMnO_4$ stain prepared by dissolving 1.5 g $KMnO_4$, 10 g potassium carbonate, and 1.25 mL 10% sodium hydroxide in 200 mL water. Flash chromatography was performed with 200–400 μ silica gel.

4.2. Materials

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Anhydrous tetrahydrofuran (THF) was purchased from Sigma Aldrich. TMSCl was distilled from CaH_2 under a positive N_2 atmosphere. Phenyllithium was purchased from Sigma Aldrich. Aryllithium reagents were prepared from the corresponding arylhalides and *t*-BuLi (1.70 M in pentane) and used in situ. *t*-BuLi (1.70 M in pentane) were commercially available and titrated using 2,6-di-*tert*-butyl-4-methylphenol and fluorene in THF. All glassware was flamed-dried under high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths were prepared using dry ice-isopropanol slush bath mixtures. All organocuprate 1,4-conjugate addition reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

4.3. General procedure A: conjugate addition reactions of lithium diarylcuprates or magnesiumbromide diarylcuprates (Ar_2CuLi or $Ar_2CuMgBr$) with thiochromones

The reaction was run at about 0.11 M concentration and was worked up after 18 h. To a flame-dried LiCl (51 mg, 1.2 mmol, 2.4 equivalent) under argon was added CuCN (54 mg, 0.6 mmol, 1.2 equivalent) and THF (1.5 mL). The resultant mixture was stirred for 10 min at room temperature and then cooled to a −78 °C followed by addition of aryl lithium or aryl magnesium bromide(1.2 mmol, 2.4 equivalent). The resultant solution was stirred for additional 30 min at −78 °C under argon, followed by addition of thiochromones [0.5 mmol mixed with TMSCl (1.0 mmol) in THF (2.0 mL)] at −78 °C. The reaction mixture was allowed to warm up to room temperature during over night stirring. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (10.0 mL) and extracted with ethyl acetate (3 × 10.0 mL). The combined organic phase was washed with brine (15.0 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 0–5% ethyl acetate in hexane, v/v) to give pure compounds.

4.4. General procedure B: conjugate addition reactions of lithium arylcyanocuprates (ArCuCNLi) with thiochromones

The reaction was run at about 0.12 M concentration and was worked up after 18 h. To a flame-dried LiCl (51 mg, 1.2 mmol, 2.4 equivalent) under argon was added CuCN (53 mg, 0.6 mmol, 1.2 equivalent) and THF (1.5 mL). The resultant mixture was stirred for 10 min at room temperature and then cooled to a −78 °C followed by addition of aryl lithium (0.6 mmol, 1.2 equivalent). The resultant solution was stirred for additional 30 min at −78 °C under argon, followed by addition of thiochromone [0.5 mmol mixed with TMSCl (1.0 mmol) in THF (2.0 mL)] at −78 °C. The reaction mixture was allowed to warm up to room temperature during over night stirring. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (10.0 mL) and extracted with ethyl acetate (3 × 10.0 mL). The combined organic phase was washed with brine (15.0 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 0–5% ethyl acetate in hexane, v/v) to give pure compounds.

4.5. General procedure C: conjugate addition reactions of aryl lithium with thiochromones in the presence of catalytic amount of CuI

The reaction was run at about 0.12 M concentration and was worked up after 18 h To a CuCN (0.30 equivalent) in THF (1.5 mL) under argon at 0 °C, was added aryl lithium (1.2 equivalent). The resultant mixture was stirred for 30 min at 0 °C and then cooled to a − 78 °C followed by addition of thiochromone [0.5 mmol mixed with TMSCl (1.0 mmol) in THF (2.0 mL)]. The reaction mixture was allowed to warm up to room temperature during over night stirring. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (10.0 mL) and extracted with ethyl acetate (3 × 10.0 mL). The combined organic phase was washed with brine (15.0 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 0–5% ethyl acetate in hexane, v/v) to give pure compounds.

4.6. General procedure D: conjugate addition reactions of phenyl lithium to thiochromones in the presence of 0.3 equivalent of 2LiCl·CuCN and TMSCl

The reaction was run at about 0.12 M concentration and was worked up after 18 h To a flame-dried LiCl (12 mg, 0.3 mmol, 0.6 equivalent) under argon was added CuCN (13 mg, 0.15 mmol, 0.3 equivalent) and THF (1.5 mL). The resultant mixture was stirred for 10 min at room temperature and then cooled to a −78 °C followed by addition of phenyl lithium (0.6 mmol, 1.2 equivalent). The resultant solution was stirred for additional 30 min at −78 °C under argon, followed by addition of thiochromones [0.5 mmol mixed with TMSCl (1.0 mmol) in THF (2.0 mL)] at −78 °C. The reaction mixture was allowed to warm up to room temperature during over night stirring. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (10.0 mL) and extracted with ethyl acetate (3 × 10.0 mL). The combined organic phase was washed with brine (15.0 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 0–5% ethyl acetate in hexane, v/v) to give pure compounds.

HRMS data for compounds **4Ad**, **4Ai**, **4Am**, **4Bg**, **4Bk**, **4Bm**, **4Cg**, **4Cm**, **4Em**, and **4Fm** were analyzed by TOF MS. Compounds **4Aa**–**Ac**, **4Ae**-**Ah**, **4Aj**-**Am**, **4Ba**, **4Ca**, **4Da**, **4Ea**, **4Fa**, **4Ga**, and **4Ha** have been fully characterized and reported.[14d,14g,15,16,19]

4.6.1. 2-Phenylthiochroman-4-one (*4Aa*)

Employing General Procedure B, using PhLi (1.9 M, 0.32 mL, 0.6 mmol) and thiochromone (81 mg, 0.5 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Aa** (98 mg, 82%): mp 55.9–56.2 °C; IR (neat) 3060 (w), 1674 (s), 1580 (s), 1489 (w), 1452 (m), 1431 (s), 1279 (s), 1237 (m), 1153 (w), 1082 (m), 752 (m), 706 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (dd, J = 3.2, 16.4 Hz, 1 H), 3.25 (dd, J = 13.2, 16.4 Hz, 1 H), 4.66 (dd, J = 3.2, 13.2 Hz, 1 H), 7.14 (ddd, J = 1.2, 7.2, 8.0 Hz, 1H), 7.22 (dd, J = 0.8, 8.0 Hz, 1H), 7.24–7.38 (m, 6H), 8.08 (dd, J = 1.2, 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.5, 46.7, 125.3, 127.3, 127.4, 128.5, 129.0, 129.3, 130.4, 133.7, 138.5, 142.1, 194.4; The data matches with literature.[14d,14g,15]

4.6.2. 2-(4-Phenylbenzene)thiochroman-4-one (*4Ad*)

Employing General Procedure A, using 4-biphenylmagnesium bromide (1.0 M, 2.4 mL, 2.4 mmol) and thiochromone (162 mg, 1.0 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Ad** (287 mg, 91%): mp 117.6–118.5 °C; IR (neat) 3031 (w), 2894 (w), 1679 (s), 1589 (w), 1486 (w), 1433 (w), 1281 (m), 1235 (w), 1085 (w), 840 (w), 759 (m), 717 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (dd, J = 3.6, 16.5 Hz, 1 H), 3.41 (dd, J = 12.6, 16.5 Hz, 1 H), 4.82 (dd, J = 3.3, 12.6 Hz, 1 H), 7.23–7.58 (m, 9H), 7.61–7.69 (m, 3 H), 8.22 (dd, J = 1.5, 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.2, 46.7, 125.3, 127.1, 127.3, 127.6, 127.7, 127.9, 128.9, 129.3, 130.5, 133.7, 137.4, 140.4, 141.5, 142.1, 194.4; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{21}H_{16}OS$, 316.0922; found 316.0918.

4.6.3. 2-(3-Methyl-4-methoxyphenyl)thiochroman-4-one (*4Ai*)

Employing General Procedure A and using thiochromone (162 mg, 1.0 mmol) and 3-Me-4-MeOPhMgBr (2.4 mL of 1.0 M, 2.40 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Ai** (243 mg, 85%): mp 67.3–68.1 °C; IR (neat) 3067 (w), 3004 (w), 2918 (w), 2839 (w), 1671 (s), 1608 (m), 1581 (m), 1503 (m), 1455 (w), 1435 (m), 1284 (m), 1254 (m), 1227 (m), 1132 (m), 1227 (m), 1132 (m), 1027 (m), 827 (m), 758 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.21 (dd, J = 3.3, 16.5 Hz, 1 H), 3.34 (dd, J = 13.2, 16.5 Hz, 1 H), 3.88 (s, 3H), 4.69 (dd, J = 3.0, 13.2 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 7.16–7.35 (m, 4H), 7.45 (ddd, J = 1.5, 7.2, 7.8 Hz, 1H), 8.19 (dd, J = 1.5, 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 45.1, 47.0, 55.4, 110.1, 125.1, 125.8, 127.2, 127.3, 129.2, 129.7, 129.9, 130.4, 133.6, 142.5, 157.8, 194.8; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{17}H_{16}O_2S$, 284.0871; found 284.0867.

*4.6.4. 2-[3,5-(Trifluoromethyl)phenyl]thiochroman-4-one (**4Am**)*

Employing General Procedure A and using thiochromone (162 mg, 1.0 mmol) and 3,5-(trifluoromethyl)PhMgBr (4.80 mL of 1.0 M, 4.80 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Am** (330 mg, 88%): mp 125–127 °C; IR (neat) 3056 (w), 2848 (w), 1677 (s), 1584 (w), 1438 (w), 1378 (w), 1278 (s), 1174 (m), 1123 (s), 1054 (w), 939 (w), 901 (m), 764 (w), 744 (w), 681 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (dd, J = 3.2, 16.4 Hz, 1 H), 3.35 (dd, J = 12.4, 16.4 Hz, 1H), 4.86 (dd, J = 3.2, 12.4 Hz, 1H), 7.23–7.34 (m, 2H), 7.47 (ddd, J = 1.6, 7.2, 8.0 Hz, 1H), 7.90 (s, 1H), 7.93 (s, 2H), 8.17 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.6, 46.1, 122.5 (p, $J_{C\text{-}F}$ = 4.0 Hz), 123.0 (q, $J_{C\text{-}F}$ = 272 Hz, CF_3), 125.9, 127.5, 127.8 (d, $J_{C\text{-}F}$ = 12 Hz), 129.4, 130.3, 132.4 (q, $J_{C\text{-}F}$ = 34.0 Hz), 134.0, 140.5, 141.1, 192.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 62.9; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{17}H_{10}OSF_6$, 376.0356; found 376.0360. The data matches with literature.[16]

*4.6.5. 6-Chloro-2-(4-methoxyphenyl)thiochroman-4-one (**4Bg**)*

Employing General Procedure A and using 6-chlorothiochromone (98 mg, 0.5 mol) and 4-MeOPhMgBr (2.4 mL of 1.0 M, 2.40 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Bg** (131 mg, 86%): mp 95.5–96.7 °C; IR (neat) 3057 (w), 2951 (w), 2924 (w), 2832 (w), 1676 (s), 1608 (m), 1580 (m), 1509 (m), 1450 (m), 1418 (w), 1297 (w), 1249 (m), 1177 (w), 1093 (w), 1023 (m), 889 (w), 820 (m), 779 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (dd, J = 3.6, 16.5 Hz, 1 H), 3.32 (dd, J = 12.3, 16.5 Hz, 1 H), 3.86 (s, 3H), 4.70 (dd, J = 3.6, 12.6 Hz, 1 H), 6.91–6.98 (m, 2H), 7.26 (d, J = 8.7 Hz, 1 H), 7.33–7.43 (m, 3 H), 8.14 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.0, 46.5, 55.4, 114.0, 128.6, 128.6, 128.8, 130.0, 131.4, 131.5, 133.6, 140.6, 160.0, 193.5; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{16}H_{13}O_2SCl$, 304.0325; found 304.0328.

*4.6.6. 6-Chloro-2-(4-fluorophenyl)thiochroman-4-one (**4Bk**)*

Employing General Procedure A and using 6-chlorothiochromone (95 mg, 0.5 mmol) and 4-FPhMgBr (1.2 mL of 1.0 M, 1.20 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Bk** (99 mg, 68%): mp 76.5–77.3 °C; IR (neat) 3040 (w) 3045 (w), 2981 (w), 1677 (s), 1603 (w), 1577 (w), 1507 (s), 1451 (m), 1389 (m), 1271 (w), 1229 (m), 1159 (w), 1094 (w), 898 (w), 862 (w), 820 (m), 792 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (dd, J = 3.9, 16.5 Hz, 1 H), 3.31 (dd, J = 12.0, 16.5 Hz, 1 H), 4.72 (dd, J = 4.2, 12.0 Hz, 1 H), 7.06–7.15 (m, 2H), 7.26 (d, J = 8.7 Hz, 1 H), 7.37–7.47 (m, 3 H), 8.14 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.8, 46.4, 116.1 (d, $J_{C\text{-}F}$ = 21.8 Hz), 128.6, 128.9, 129.2 (d, $J_{C\text{-}F}$ = 7.5 Hz), 131.4, 131.6, 133.7, 133.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 140.1, 162.6 (d, $J_{C\text{-}F}$ = 247 Hz), 193.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ - 112.7 (septet, J = 5.64 Hz); HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{15}H_{10}OSFCl$, 292.0125; found 292.0123.

*4.6.7. 6-Chloro-2-[3,5-(trifluoromethyl)phenyl]thiochroman-4-one (**4Bm**)*

Employing General Procedure A and using 6-chlorothiochromone (70 mg, 0.36 mmol) and 3,5-(trifluoromethyl)PhMgBr (3.46 mL of 0.5 M, 1.73 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Bm** (105 mg, 71%): mp 97.1–98.0 °C; IR (neat) 3090 (w), 2922 (m), 2851 (w), 1679 (s), 1582 (w), 1455 (w), 1378 (m), 1278 (s), 1169 (s), 1120 (s), 1053 (m), 938 (w), 901 (m), 846 (w), 823 (w), 704 (w), 682 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 (dd, J = 3.6, 16.4 Hz, 1 H), 3.37 (dd, J = 12.0, 16.4 Hz, 1H), 4.86 (dd, J = 3.6, 12.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 2.4, 8.4 Hz, 1H), 7.92 (s, 3H), 8.16 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.6, 45.7, 122.8 (p, $J_{C\text{-}F}$ = 3.7 Hz), 122.9 (q, $J_{C\text{-}F}$ = 271 Hz, CF_3), 127.8 (d, $J_{C\text{-}F}$ = 12.5 Hz), 128.7, 129.1, 131.3, 132.2, 132.6 (q, $J_{C\text{-}F}$ = 34 Hz), 134.0, 138.8, 140.6, 191.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 62.9; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{17}H_9OSF_6Cl$, 409.9967; found 409.9962.

*4.6.8. 6-Bromo-2-(4-methoxyphenyl)thiochroman-4-one (**4Cg**)*

Employing General Procedure A and using 6-bromothiochromone (73 mg, 0.3 mmol) and 4-MeOPhMgBr (0.72 mL of 1.0 M, 0.72 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Cg** (92 mg, 88%): mp 101.0–102.1 °C; IR (neat) 3052 (w), 2925 (w), 2831 (w), 1676 (s), 1609 (m), 1573 (m), 1509 (m), 1453 (w), 1417 (w), 1305 (w), 1248 (m), 1176 (w), 1111 (w), 1090 (w), 1022 (w), 832 (w), 820 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (dd, J = 3.6, 16.5 Hz, 1 H), 3.28 (dd, J = 12.6, 16.5 Hz, 1 H), 3.82 (s, 3H), 4.67 (dd, J = 3.6, 12.6 Hz, 1 H), 6.91 (dd, J = 1.8, 6.9 Hz, 1 H), 7.16 (d, J = 8.7 Hz, 1 H), 7.34 (dd, J = 1.8, 6.9 Hz, 1 H), 7.51 (dd, J = 2.4, 8.4 Hz, 1 H), 8.26 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.9, 46.5, 55.4, 114.4, 118.9, 128.6, 128.8, 130.0, 131.7, 131.8, 136.4, 141.2, 159.7, 193.3; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{16}H_{13}O_2SBr$, 347.9820; found 347.9818.

*4.6.9. 6-Bromo-2-[3,5-(trifluoromethyl)phenyl]thiochroman-4-one (**4Cm**)*

Employing General Procedure A and using 6-bromothiochromone (100 mg, 0.41 mmol) and 3,5-(trifluoromethyl)PhMgBr (1.96 mL of 0.5 M, 0.98 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Cm** (165 mg, 82%): mp 101.2–102.5 °C; IR (neat) 3079 (w), 2923 (w), 2853 (w), 1679 (s), 1572 (w), 1454 (w), 1379 (m), 1343 (w), 1276 (s), 1227 (m), 1166 (s), 1121 (s), 1110 (s), 1048 (w), 914 (w), 845 (w), 702 (w) 683 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.17 (dd, J = 4.2, 16.5 Hz, 1 H), 3.26 (dd, J = 11.7, 16.5 Hz, 1H), 4.75 (dd, J = 3.9, 12.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.49 (dd, J = 2.1, 8.4 Hz, 1H), 7.82 (s, 3H), 8.19 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 45.7, 119.8, 122.8 (p, $J_{C\text{-}F}$ = 3.8 Hz), 123.0 (q, $J_{C\text{-}F}$ = 271 Hz, CF_3), 127.8 (d, $J_{C\text{-}F}$ = 3.85 Hz), 128.8, 131.5, 132.1, 132.6 (q, $J_{C\text{-}F}$ = 33.8 Hz), 136.8, 139.4, 140.6, 191.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ - 62.9; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{17}H_9OSF_6Br$, 453.9462; found 453.9459.

*4.6.10. 6-Methyl-2-[3,5-(trifluoromethyl)phenyl]thiochroman-4-one (**4Em**)*

Employing General Procedure A and using 6-methylthiochromone (95 mg, 0.5 mmol) and 3,5-(trifluoromethyl) PhMgBr (4.80 mL of 0.5 M, 2.40 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave light yellow solid **4Em** (163 mg, 84%): mp 106.1–107.2 °C; IR (neat) 3040 (w), 2956 (m), 2928 (m), 2870 (w), 1676 (s), 1600 (w), 1464 (w), 1376 (s), 1349 (w), 1275 (s), 1239 (w), 1166 (s), 1123 (s), 939 (w), 900 (m), 845 (w), 817 (w), 703 (m), 680 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.16 (dd, J = 3.6, 16.4 Hz, 1 H), 3.25 (dd, J = 12.4, 16.4 Hz, 1H), 4.73 (dd, J = 3.2, 12.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.21 (ddd, J = 0.4, 2.0, 8.0 Hz, 1 H), 7.79 (s, 1H), 7.82 (s, 2H), 7.90 (dd, J = 0.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 44.6, 46.2, 122.5 (p, $J_{C\text{-}F}$ = 4.0 Hz), 123.0 (q, $J_{C\text{-}F}$ = 271 Hz, CF_3), 127.2, 127.8 (d, $J_{C\text{-}F}$ = 2.6 Hz), 129.5, 130.1, 132.4 (q, $J_{C\text{-}F}$ = 32.0 Hz), 135.2, 135.9, 137.1, 141.2, 193.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ - 62.9; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{18}H_{12}OSF_6$, 390.0513; found 390.0518.

*4.6.11. 6,7-Dimethyl-2-[3,5-(trifluoromethyl)phenyl]thiochroman-4-one (**4Fm**)*

Employing General Procedure A and using 6,7-dimethylthiochromone (95 mg, 0.5 mmol) and 3,5-(trifluoromethyl)PhMgBr (4.80 mL of 0.5 M, 2.40 mmol), after purification by flash column chromatography (silica, 0–5% Ethyl acetate: hexanes, v/v) gave

light yellow solid **4Fm** (165 mg, 82%): mp 111.5–112.6 °C; IR (neat) 3035 (w), 2954 (m) 2923 (m), 2854 (m), 1672 (s), 1599 (s), 1474 (m), 1463 (m), 1337 (w), 1275 (s), 1169 (s), 1123 (s), 1050 (w), 938 (w), 899 (s), 861 (w) 702 (m), 682 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.20 (s, 1H), 3.11 (dd, $J = 3.6, 16.5$ Hz, 1 H), 3.22 (dd, $J = 12.0, 16.5$ Hz, 1H), 4.71 (dd, $J = 3.6, 12.0$ Hz, 1H), 6.98 (s, 1H), 7.78 (s, 1H), 7.81 (s, 2H), 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.1, 44.7, 46.1, 122.4 (p, $J_{C-F} = 3.8$ Hz), 123.0 (q, $J_{C-F} = 271$ Hz, CF_3), 127.8 (d, $J_{C-F} = 3.8$ Hz), 128.2, 128.5, 130.0, 132.4 (q, $J_{C-F} = 33.8$ Hz), 135.0, 137.4, 141.4, 144.5, 192.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ - 62.9; HRMS (EI-ion trap) m/z: $[M]^+$ calcd for $C_{19}H_{14}OSF_6$, 404.0669; found 404.0666.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.08.012.

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