

Article

Conjugate Addition of Grignard Reagents to Thiochromones Catalyzed by Copper Salts: A Unified Approach to Both 2-Alkylthiochroman-4-One and Thioflavanone

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Academic Editors: Roman Dembinski and Igor Alabugin

Received: 8 April 2020; Accepted: 29 April 2020; Published: 1 May 2020



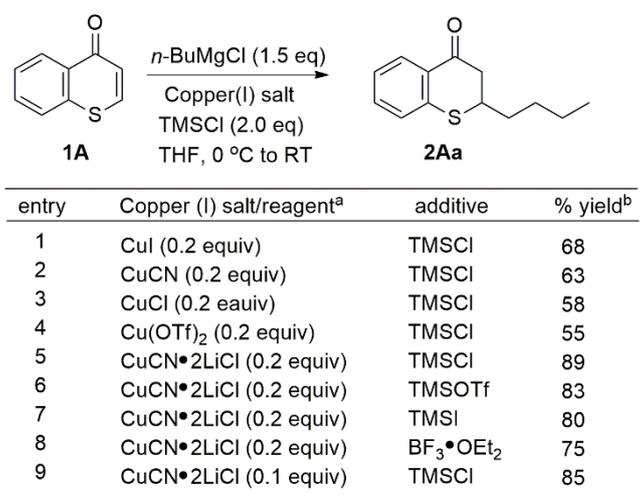
Abstract: Grignard reagents undergo conjugate addition to thiochromones catalyzed by copper salts to afford 2-substituted-thiochroman-4-ones, both 2-alkylthiochroman-4-ones and thioflavanones (2-arylthiochroman-4-ones), in good yields with trimethylsilyl chloride (TMSCl) as an additive. The best yields of 1,4-adducts can be attained with CuCN·2LiCl as the copper source. Excellent yields of 2-alkyl-substituted thiochroman-4-ones and thioflavanones (2-aryl substituted) are attained with a broad range of Grignard reagents. This approach works well with both alkyl and aromatic Grignard reagents, thus providing a unified synthetic approach to privileged 2-substituted thiochroman-4-ones and a potential valuable precursor for further synthetic applications towards many pharmaceutically active molecules. The use of commercially available and/or readily prepared Grignard reagents will expedite the synthesis of a large library of both 2-alkyl substituted thiochroman-4-ones and thioflavanones for additional synthetic applications.

Keywords: conjugate addition; thiochroman-4-ones; Grignard reagents; thiochromones; thioflavanones; 2-alkylthiochroman-4-ones

1. Introduction

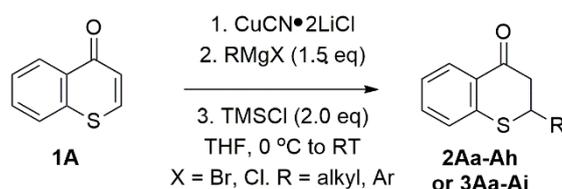
The 1,4-conjugate addition reaction of organometallic reagents, including Grignard reagents, is one of the most reliable carbon–carbon bond formation reaction in organic synthesis. [1] Without the addition of catalysts, such as Cu (I) salts, Grignard reagents usually undergo 1,2-addition to α , β -unsaturated carbonyl compounds. It has been shown that with the addition of Cu(I) salts, Grignard reagents undergo exclusive 1,4-conjugate addition to carbonyl compounds to afford 1,4-adducts [1,2]. In this investigation, we aimed to develop a unified approach to a broad scope of 2-substituted thiochroman-4-ones by taking advantage of the ease in preparation and the breadth in the scope of Grignard reagents. Sulfur-containing heterocycles are widely present in numerous pharmaceutical active molecules as well as in many bioactive natural products [3–6], with widespread applications in areas, such as material science, biology, medicinal chemistry, and food chemistry, in recent years [7–13]. Although the isosteric replacement of an oxygen atom by a sulfur atom is expected to improve

such as TMSCl, was needed in the conjugate addition of organolithium reagents to thiochromones using a stoichiometric amount of copper salts as no desired 1,4-adducts were observed in the absence of a Lewis acid activator [66,67]. A modest yield of 1,4-adduct 2-*n*-butylthiochroman-4-one **2Aa** was formed with *n*-BuMgCl and a 0.2 equivalent of CuI or CuCN with TMSCl as the activator (Scheme 1, entries 1–2). The use of CuCl did not improve the yield (Scheme 1, entry 3). With the addition of LiCl to CuCN, an excellent yield of 2-*n*-butylthiochroman-4-one **2Aa** was achieved in the presence of TMSCl (Scheme 1, entry 5, 89%). Other Lewis acids, such as TMSOTf, TMSI, and BF₃·OEt₂, also activated this reaction but were not better activators than TMSCl as they did not offer better yields (Scheme 1, entries 6–8). These results show that the use of 0.2 equivalent of CuCN·2LiCl and TMSCl offered the highest yield. We also found that CuCN·2LiCl can be further reduced to 0.1 equivalent and a comparable yield of **2Aa** could be attained (Scheme 1, entry 9, 85%).



Scheme 1. Optimization of 1,4-conjugate addition of *n*-butyl magnesium chloride to thiochromone. a. Reagents were prepared by adding *n*-BuMgCl to copper salts in THF. b. Yields are based on isolated products by column chromatography.

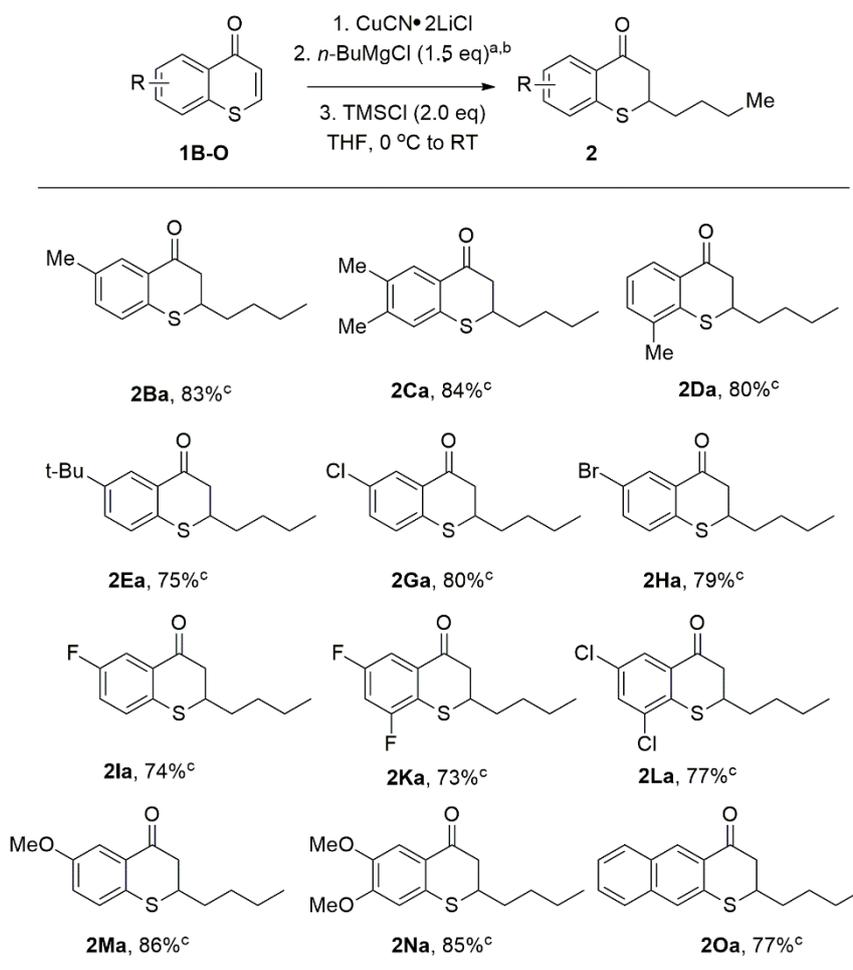
With the optimal reaction condition in hand, the scope of the Grignard reagents was explored (Scheme 2, 64–90%). It was found that a broad range of Grignard reagents underwent conjugate addition to thiochromone **1A** to afford 1,4-adducts **2Aa–Ah** and **3Aa–Ai** with good reaction yields (Scheme 2). Simple Grignard reagents, such as methyl, ethyl, *n*-butyl, and *n*-hexyl Grignard reagents, were added to **1A** smoothly to afford 1,4-adducts with excellent efficiency (Scheme 2, 75–88%). Steric bulkier Grignard reagents, such as *i*-Pr, *t*-butyl Grignard reagents, gave lower yields (Scheme 2, **2Ae**, 69% and **2Af**, 64%). Cyclic Grignard reagents were also tolerated to give good yields of 1,4-adducts (Scheme 2, **2Ag**, 82% and **2Ah**, 85%). Aromatic Grignard reagents also reacted very well under these optimal reaction conditions. PhMgBr was added to thiochromone **1A** to offer 1,4-adduct **3Aa** in an 89% yield. Grignard reagents with electron-donating groups on the aromatic ring were also found to work well (Scheme 2, **3Ab–Ad**, 80–90%). Grignard reagents with strong electron-withdrawing groups on the aromatic ring were also tolerated (Scheme 2, **3Ae**, 70%). Grignard reagents prepared from extended aryl bromides, such as 2-bromonaphthalene and 9-bromophenanthrene, were also added to thiochromone **1A** smoothly with high yields (Scheme 2, **3Af**, 84%; **3Ag**, 78%). To our delight, Grignard reagents prepared from aromatic heterocycles also worked well. Both (2-furyl)magnesium bromide and 2-thienylmagnesium bromide were added to thiochromone **1A** to afford corresponding 1,4-adducts in good yields (Scheme 2, **3Ah**, 79%; **3Ai**, 75%).



entries ^a	R ^b	Product	yield ^c
1	<i>n</i> -Bu	2Aa	88%
2	Me	2Ab	75%
3	Et	2Ac	79%
4	Hexyl	2Ad	86%
5	<i>i</i> -Pr	2Ae	69%
6	<i>t</i> -Bu	2Af	64%
7	cyclopropyl	2Ag	82%
8	cyclohexyl	2Ah	85%
9	C ₆ H ₅	3Aa	89%
10	2-MeC ₆ H ₄	3Ab	80%
11	4-MeOC ₆ H ₄	3Ac	90%
12	2-MeOC ₆ H ₄	3Ad	83%
13	3,5-(CF ₃) ₂ C ₆ H ₃	3Ae	70%
14	2-Naphthyl	3Af	84%
15	9-phenanthryl	3Ag	78%
16	furyl	3Ah	79%
17	thienyl	3Ai	75%

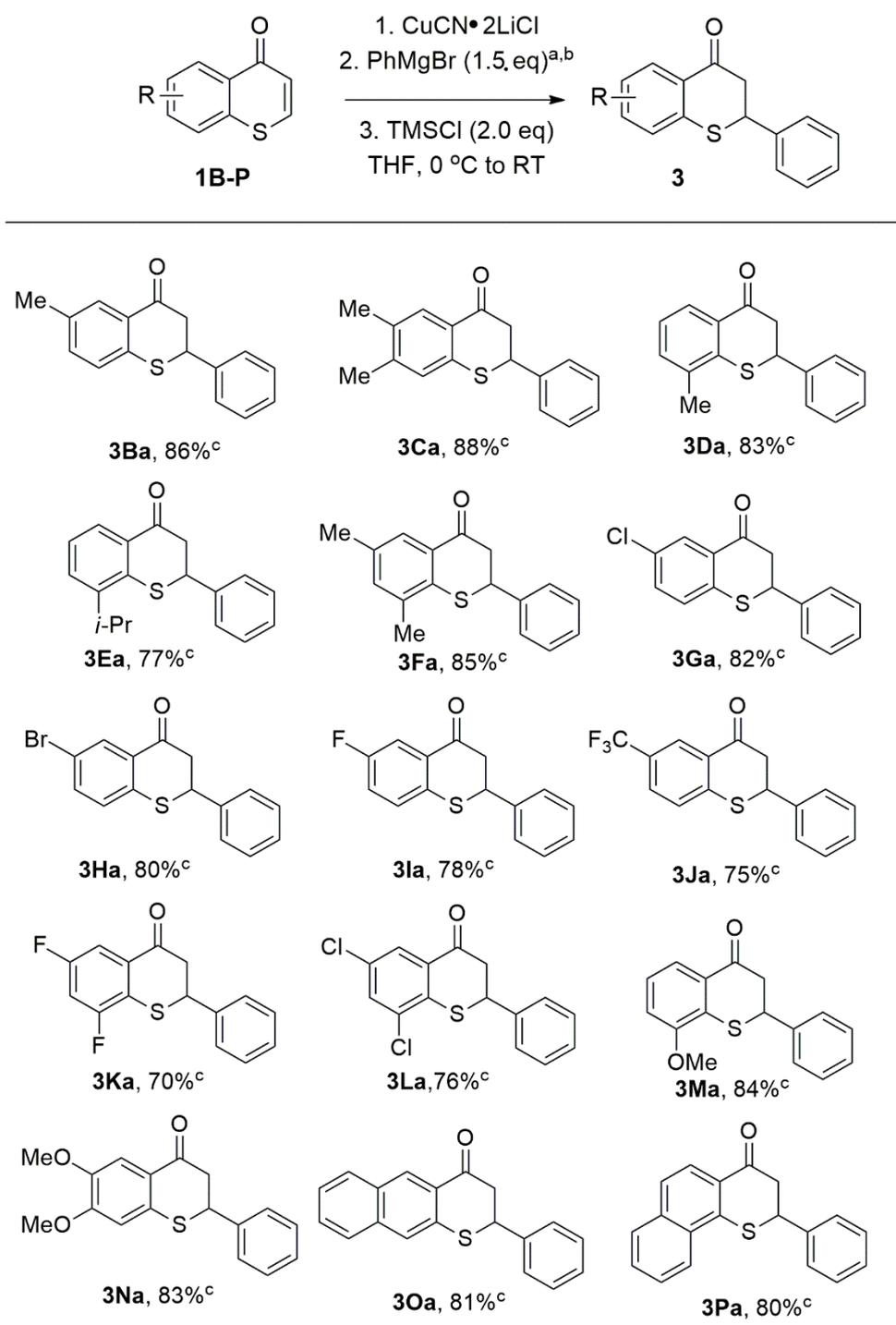
Scheme 2. The scope of Grignard reagents in conjugate addition to thiochromone. a. All the reactions were performed using 1.5 equiv of RMgX in the presence of 2.0 equiv of TMSCl unless noted otherwise. b. RMgX were commercially available or prepared from corresponding RX in THF and used as a THF solution. c. Yields are based on isolated products by column chromatography.

With the optimal reaction addition for conjugate addition to thiochromone **1A** in hand, we next investigated the scope of thiochromone substrates for the conjugate addition of Grignard reagents. A number of substituted thiochromones **1B–1O** were investigated. It was found that *n*-butylmagnesium chloride readily added to the substituted thiochromones **1B–1O** to afford 1,4-adducts **2Ba–2Oa** with good yields (Scheme 3, 73–86%). Thiochromones bearing simple alkyl groups, such as a methyl group, reacted with *n*-BuMgCl to afford **2Ba–2Da** in good yields under the optimal reaction condition (Scheme 3, 80–84%). The bulky *t*-butyl group was also tolerated to afford 1,4-adduct **2Ea** with good yield. Thiochromones with halides, such as F, Br, and Cl, also reacted smoothly with *n*-BuMgCl (Scheme 3, 74–80%). Thiochromones with two halides on the aromatic ring, such as 6,8-difluorothiochromanone and 6,8-dichlorothiochromone, were also tolerated (Scheme 3, **2Ka**, 73% and **2La**, 77%). Electron-donating groups, such as MeO-, also worked well to afford 1,4-adduct **2Ma** and **2Na** in higher yields (Scheme 3). Thiochromane **1O** with an extended aromatic structure also underwent conjugate addition with *n*-BuMgCl to afford 1,4-adduct **2Oa** in a 77% yield (Scheme 3).



Scheme 3. Scope of the substituted thiochromones with $n\text{-BuMgCl}$. a. All the reactions were performed using 1.5 equiv of BuMgCl in the presence of 2.0 equiv of TMSCl unless noted otherwise. b. RMgX were commercially available or prepared from corresponding RX in THF and used as a THF solution. c. Yields are based on isolated products by column chromatography.

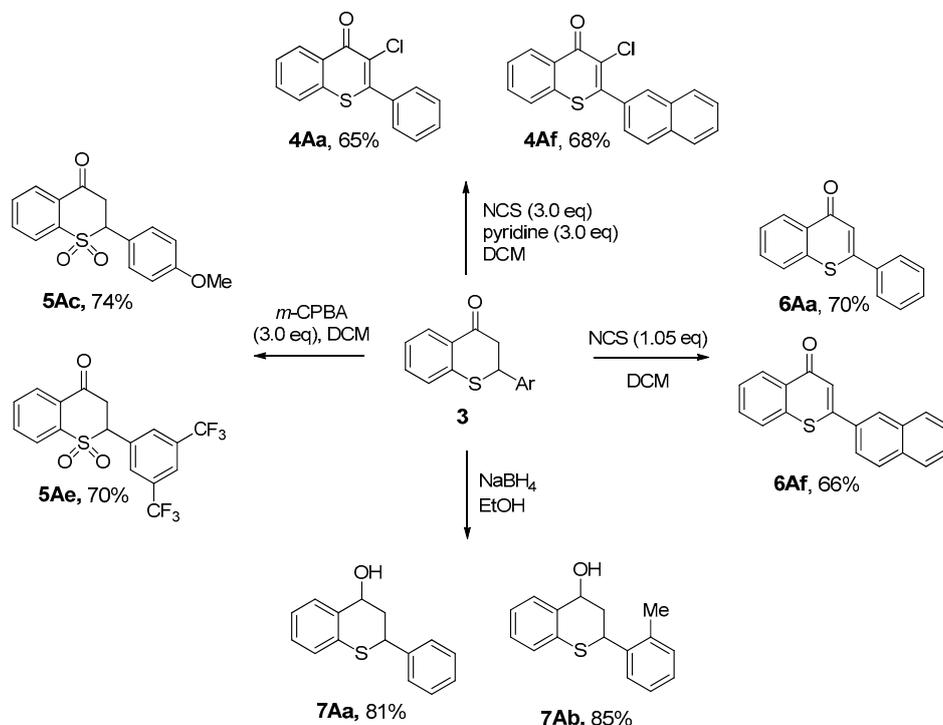
The scope of thiochromones was also explored with PhMgBr to synthesize various thioflavanones. Phenylmagnesium bromide underwent conjugate addition to thiochromones **1B–1P** smoothly to furnish thioflavanones with good yields (Scheme 4). It was found that thiochromones with simple alkyl groups, such as methyl, on the aromatic ring reacted smoothly with PhMgBr to afford 1,4-adduct in good yields (Scheme 4, 83–88%). Bulky groups (*i*-Pr) were also tolerated (Scheme 4, **3Ea**, 77%). PhMgBr also underwent conjugate addition to thiochromones with halides F, Br, and Cl on the aromatic ring with high efficiency (Scheme 4, 78–82%). Thiochromones with two halides on the aromatic ring, such as 6,8-difluorothiochromanone and 6,8-dichlorothiochromone, were also tolerated to afford good yields of 1,4-adduct (Scheme 4, **3Ka**, 70% and **3La**, 76%). Electron-donating groups, such as MeO- , were also tolerated to furnish 1,4-adducts in an excellent yield (Scheme 4, **3Ma**, 84% and **3Na**, 83%). The steric hindrance was not a problem as PhMgBr adds to 8-substituted thiochromone (8-MeO-, 8-*i*-Pr) with high yields (Scheme 4). PhMgBr also underwent conjugate addition to thiochromones with extended aromatic structures with high efficiency (Scheme 4, **3Oa**, 81%; **3Pa**, 80%).



Scheme 4. Reactions of PhMgBr with substituted thiochromones. a. All the reactions were performed using 1.5 equiv of PhMgBr in the presence of 2.0 equiv of TMSCl unless noted otherwise. b. PhMgBr were commercially available. c. Yields are based on isolated products by column chromatography.

Thiochromanones, i.e., thiochroman-4-ones, 2-alkylthiochroman-4-ones, and thioflavanones (2-arylthioflavanones), are valuable synthons and vital precursors in organic synthesis for bioactive thiochromanone derivatives. [31–38] In our previous investigation, 2-alkylthiochroman-4-ones were successfully converted into other useful thiochroman-4-one derivatives for additional synthetic application [66]. The 1,4-adducts-thioflavones can also be utilized for further synthetic applications towards 2-aryl substituted thiochroman-4-one derivatives (Scheme 5). For example, thioflavanone **3** was

converted to chlorinated thiochromone **4** upon treatment with excess *N*-chlorosuccinimide and pyridine (Scheme 5, **4Aa**, 65%; **4Af**, 68%). It was also oxidized to sulfone **5** with excess *m*-chloroperobenzoic acid (*m*-CPBA) in dichloromethane (Scheme 5, **5Ac**, 74%; **5Ae**, 70%). After treatment with *N*-chlorosuccinimide (NCS, 1.0 equivalent), thioflavanone **3** was transformed to thiochromone **6** with good yields (Scheme 5, **6Aa**, 70%; **6Af**, 66%). It was also reduced by sodium borohydride to the corresponding alcohol **7** (Scheme 3, **7Aa**, 81%; **7Ab**, 85%).



Scheme 5. Synthetic applications of thioflavanones.

3. Materials and Methods

3.1. General Methods

The ^1H , ^{13}C , and ^{19}F -NMR spectra were recorded on a BRUKER AscendTM 400 NMR spectrometer (Bruker Corporation, Billerica, MA, USA), operating at 400 MHz for ^1H and 100 MHz for ^{13}C and 376 MHz for ^{19}F . Samples for NMR spectra were dissolved in deuterated chloroform unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 60 mesh, with an 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 of 10% sodium hydroxide in 200 mL of water. Flash chromatography was performed with 230–400 mesh silica gel. Infrared (IR) spectra were recorded on a Nicolet iS10 FT-IR spectrometer (Thermo Scientific, Waltham, MA, USA) as neat samples (thin films).

3.2. Materials

Solvents and chemicals were obtained from commercial sources and used without further purification unless stated otherwise. Anhydrous tetrahydrofuran (THF) was purchased from Sigma Aldrich (Sigma-Aldrich, St. Louis, MO, USA). TMSCl was distilled from CaH_2 under a positive N_2 atmosphere. Grignard reagents were purchased from Sigma Aldrich or prepared from the corresponding bromocompounds. All glassware was flamed-dried under high vacuum and purged with argon to cool to room temperature. Low-temperature baths were prepared using dry ice-isopropanol slush

bath mixtures. All 1,4-conjugate addition reactions with Grignard reagents were conducted under a positive dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

3.3. General Procedure A: Conjugate Addition Reactions of Grignard Reagents (RMgX or ArMgX; X = Cl or Br) to Thiochromones Catalyzed by CuCN·2LiCl (0.2 eq)

To flame-dried LiCl (8.5 mg, 0.2 mmol, 0.4 equivalent) under argon, CuCN (9.0 mg, 0.1 mmol, 0.2 equivalent) and THF (1.0 mL) were added. The resultant mixture was stirred for 10 min at room temperature and then cooled to 0 °C followed by the addition of a Grignard reagent (0.75 mmol, 1.5 equivalent). The resultant solution was stirred for an additional 30 min at 0 °C under argon and then thiochromones [0.5 mmol mixed with TMSCl (1.0 mmol) in THF 1.0 mL] were added. The reaction mixture was allowed to warm up to room temperature during overnight stirring. Then, the reaction mixture was quenched with saturated aqueous NH₄Cl (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 Na₂SO₄, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 0–2% ethyl acetate in hexane, *v/v*) to give pure compounds.

3.4. Synthesis

HRMS data for compounds **2Ag**, **3Ag**, **2Ka**, **2La**, **2Na**, **3Ea**, **3Fa**, **3Ka–3Ma**, **3Pa**, **4Af**, **5Ac**, **5Ae**, and **7Ab** were analyzed by TOF MS. Compounds **2Aa–2Af** [66], **2Ah** [65], **2Ba–2Ia** [66], **2Ma** [66], **2Oa** [66], **3Aa–3Af** [51,67], **3Ah–3Ai** [51,59], **3Ba–3Da** [51,67], **3Ga–3Ja** [51,67], **3Ma** [51], **3Na** [58], **3Oa** [51,67], **4Aa** [68], **6Aa** [69], **6Af** [70], and **7Aa** [59] have been fully characterized and reported. (Supplementary materials)

3.4.1. Synthesis of 2-Cyclopropylthiochroman-4-one (**2Ag**)

Employing General Procedure A, using cyclopropylmagnesium bromide (1.0 M, 1.0 mL, 1.0 mmol) and thiochromone (81 mg, 0.5 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a light-yellow solid **2Ag** (84 mg, 82%): mp 83–84 °C; IR (neat) 3056 (w), 3001 (w), 2921 (w), 1671 (s), 1590 (s), 1456 (w), 1434 (s), 1394 (w), 1284 (s), 1229 (m), 1154 (w), 1068 (w), 1023 (w), 954 (w), 759 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.22–0.29 (m, 1 H), 0.29–0.35 (m, 1 H), 0.55–0.65 (m, 2 H), 0.95–1.07 (m, 1 H), 2.70 (ddd, *J* = 2.80, 9.60, 11.6 Hz, 1 H), 2.88 (dd, *J* = 11.6, 16.4 Hz, 1 H), 3.08 (dd, *J* = 2.8, 16.4 Hz, 1 H), 7.09 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.20 (ddd, *J* = 0.4, 1.2, 8.0 Hz, 1H), 7.31 (ddd, *J* = 1.6, 7.2, 8.0 Hz, 1H), 8.01 (ddd, *J* = 0.4, 1.6, 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 4.7, 5.0, 15.4, 46.4, 47.2, 124.8, 127.5, 129.0, 130.6, 133.5, 142.1, 194.7; HRMS (EI-ion trap) *m/z*: [M + 1]⁺ calcd for C₁₂H₁₃OS, 205.0687; found 205.0679.

3.4.2. Synthesis of 2-(9-Phenanthryl)thiochroman-4-one (**3Ag**)

Employing General Procedure A, using 9-phenanthrenylmagnesium bromide (1.0 M, 1.0 mL, 1.0 mmol) and thiochromone (81 mg, 0.50 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a yellow solid **3Ag** (133 mg, 78%): mp 180–181 °C; IR (neat) 3062 (w), 2922 (w), 1668 (s), 1582 (m), 1450 (w), 1439 (w), 1295 (m), 1089 (w), 892 (w), 760 (w), 746 (m), 722 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.38 (dd, *J* = 2.8, 16.4 Hz, 1 H), 3.56 (dd, *J* = 12.8, 16.4 Hz, 1 H), 5.44 (dd, *J* = 2.8, 12.8 Hz, 1 H), 7.19 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.37 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H), 7.54 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 7.57–7.65 (m, 3H), 7.80–7.85 (m, 2H), 8.13–8.19 (m, 2H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.69 (dd, *J* = 1.2, 8.0 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 41.2, 46.2, 122.5, 123.6, 123.7, 125.4, 126.0, 126.9, 127.1, 127.4, 127.5, 129.0, 129.4, 129.5, 130.3, 130.5, 131.0, 131.04, 132.3, 133.7, 142.2, 194.9; HRMS (EI-ion trap) *m/z*: [M + 1]⁺ calcd for C₂₃H₁₇OS, 341.1000; found 341.1014.

3.4.3. Synthesis of 6,8-Difluoro-2-*n*-butylthiochroman-4-one (**2Ka**)

Employing General Procedure A, using *n*-butylmagnesium chloride (1.71 M, 0.44 mL, 0.75 mmol) and thiochromone (99 mg, 0.50 mmol), after purification by flash column chromatography (silica gel,

0–2% ethyl acetate: hexanes, *v/v*), gave a light-yellow oil **2Ka** (93 mg, 73%): IR (neat) 3083 (w), 2958 (s), 2929 (s), 2858 (s), 1686 (s), 1611 (m), 1571 (m), 1437 (m), 1571 (m), 1437 (s), 1326 (s), 1281 (s), 1217 (w), 1112 (m), 997 (m), 878 (w), 856 (w), 641 (w), 620 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.85 (t, $J = 7.2$ Hz, 3 H), 1.22–1.33 (m, 2H), 1.34–1.47 (m, 2H), 1.67 (q, $J = 7.8$ Hz, 2 H), 2.75 (dd, $J = 11.2, 16.4$ Hz, 1 H), 2.99 (dd, $J = 2.8, 16.4$ Hz, 1 H), 3.36–3.46 (m, 1H), 6.93 (ddd, $J = 2.8, 8.0, 9.2$ Hz, 1H), 7.57 (ddd, $J = 1.2, 2.8, 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 22.3, 28.7, 34.1, 41.1, 45.9, 108.7 (t, $J = 26$ Hz), 110.9 (dd, $J = 3.0, 22$ Hz), 125.4 (dd, $J = 3.0, 18$ Hz), 132.6 (dd, $J = 3.0, 7.0$ Hz), 158.6 (dd, $J = 11, 246$ Hz), 159.7 (dd, $J = 11, 246$ Hz), 192.6; ^{19}F NMR (376 MHz, CDCl_3) δ -107.4 (dd, $J = 6.4, 8.7$ Hz), -114.1 (dt, $J = 6.3, 8.3$ Hz); HRMS (EI-ion trap) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{ONaSF}_2$, 279.0631; found 279.0642.

3.4.4. Synthesis of 6,8-Dichloro-2-*n*-butylthiochroman-4-one (**2La**)

Employing General Procedure A, using *n*-butylmagnesium chloride (1.71 M, 0.32 mL, 0.54 mmol) and thiochromone (83 mg, 0.36 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a light-yellow oil **2La** (80 mg, 77%): IR (neat) 3067 (w), 2956 (m), 2928 (m), 2858 (m), 1686 (s), 1571 (m), 1538 (w), 1465 (w), 1426 (w), 1397 (s), 1285 (w), 1244 (m), 1120 (w), 1053 (w), 873 (w), 812 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.85 (t, $J = 7.2$ Hz, 3 H), 1.23–1.33 (m, 2H), 1.35–1.46 (m, 2H), 1.68 (q, $J = 7.2$ Hz, 2 H), 2.72 (dd, $J = 11.2, 16.4$ Hz, 1 H), 2.96 (dd, $J = 3.2, 16.4$ Hz, 1 H), 3.34–3.43 (m, 1H), 7.43 (d, $J = 2.4$ Hz, 1H), 7.93 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 22.3, 28.6, 34.1, 40.8, 44.8, 127.2, 130.6, 132.4, 132.7, 133.5, 139.7, 192.9; HRMS (EI-ion trap) m/z : $[\text{M} - 1]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{OSCl}_2$, 287.0064; found 287.0067.

3.4.5. Synthesis of 6,7-Dimethoxy-2-*n*-butylthiochroman-4-one (**2Na**)

Employing General Procedure A, using *n*-butylmagnesium chloride (1.71 M, 0.27 mL, 0.47 mmol) and thiochromone (69 mg, 0.31 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a light-yellow oil **2Na** (74 mg, 85%): IR (neat) 3077 (w), 3000 (w), 2954 (s), 2927 (s), 2853 (s), 1660 (s), 1591 (s), 1498 (s), 1462 (m), 1436 (m), 1388 (s), 1352 (m), 1258 (s), 1210 (s), 1177 (m), 1146 (m), 1098 (w), 1033 (s), 872 (w), 796 (w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.84 (t, $J = 7.2$ Hz, 3 H), 1.22–1.31 (m, 2H), 1.32–1.43 (m, 2H), 1.64 (q, $J = 7.2$ Hz, 2 H), 2.66 (dd, $J = 11.2, 16.4$ Hz, 1 H), 2.92 (dd, $J = 3.2, 16.4$ Hz, 1 H), 3.35–3.46 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 6.61 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 22.3, 28.9, 34.1, 42.3, 46.0, 56.0, 56.2, 109.0, 110.2, 123.9, 135.6, 147.1, 153.8, 193.6; HRMS (EI-ion trap) m/z : $[\text{M} + 1]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{O}_3\text{S}$, 281.1211; found 281.1210.

3.4.6. Synthesis of 6-Isopropyl-2-phenylthiochroman-4-one (**3Ea**)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.25 mL, 0.71 mmol) and thiochromone (95 mg, 0.47 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a yellow solid **3Ea** (102 mg, 77%): mp 78–79 °C; IR (neat) 3056 (w), 2965 (s), 2927 (m), 1673 (s), 1576 (m), 1489 (w), 1451 (w), 1411 (m), 1286 (w), 1262 (s), 1147 (w), 1973 (w), 1042 (w), 780 (w), 766 (w), 731 (w), 698 (w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.24 (d, $J = 6.8$ Hz, 3 H), 1.31 (d, $J = 6.8$ Hz, 3 H), 3.23 (dd, $J = 2.8, 16.4$ Hz, 1 H), 3.26–3.34 (m, 1H), 3.35 (dd, $J = 13.6, 16.4$ Hz, 1 H), 4.66 (dd, $J = 2.8, 13.6$ Hz, 1 H), 7.25 (dd, $J = 7.6, 15.2$ Hz, 1H), 7.34–7.51 (m, 6H), 8.09 (dd, $J = 1.6, 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.7, 23.1, 30.3, 44.9, 46.3, 124.8, 127.2, 127.5, 128.5, 129.0, 130.3, 130.9, 138.7, 140.4, 145.8, 195.1; HRMS (EI-ion trap) m/z : $[\text{M} + 1]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{OS}$, 283.1157; found 283.1147.

3.4.7. Synthesis of 6,8-Dimethyl-2-phenylthiochroman-4-one (**3Fa**)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.13 mL, 0.35 mmol) and thiochromone (42.8 mg, 0.23 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, *v/v*), gave a white solid **3Fa** (52.5 mg, 85%): mp 123–124 °C; IR (neat) 3041 (w), 2977 (w), 2922 (m), 2852 (w), 1670 (s), 1600 (m), 1456 (m), 1421 (w), 1371 (w), 1310 (m), 1280 (m), 1250 (m), 1125 (w), 871 (m), 781 (m), 706 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.09 (s, 3 H), 2.14 (s, 3

H), 2.98 (dd, $J = 3.2, 16.4$ Hz, 1 H), 3.11 (dd, $J = 13.2, 16.4$ Hz, 1 H), 4.45 (dd, $J = 2.8, 13.2$ Hz, 1 H), 6.98 (dd, $J = 0.8, 1.6$ Hz, 1 H), 7.12–7.23 (m, 3 H), 7.24–7.28 (m, 2 H), 7.68 (dd, $J = 0.8, 1.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.9, 20.7, 44.9, 46.3, 127.1, 127.5, 128.5, 129.0, 130.4, 134.1, 135.0, 136.1, 138.3, 138.8, 195.1; HRMS (EI-ion trap) m/z : $[\text{M} + 1]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{OS}$, 269.1000; found 269.0999.

3.4.8. Synthesis of 6,8-Difluoro-2-phenylthiochroman-4-one (3Ka)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.16 mL, 0.44 mmol) and thiochromone (58 mg, 0.293 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, v/v), gave a light-yellow solid **3Ka** (57 mg, 70%): mp 70–71 °C; IR (neat) 3076 (s), 3031 (w), 2959 (w), 2892 (w), 1685 (s), 1609 (m), 1571 (m), 1438 (m), 1322 (m), 1282 (m), 1130 (w), 995 (m), 879 (w), 772 (w), 697 (w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.01 (dd, $J = 0.4, 3.2$ Hz, 1 H), 3.14 (dd, $J = 13.2, 16.4$ Hz, 1 H), 4.48 (dd, $J = 3.2, 13.2$ Hz, 1 H), 6.83 (ddd, $J = 2.8, 8.0, 8.8$ Hz, 1H), 7.13–7.26 (m, 5H), 7.51 (ddd, $J = 1.6, 2.8, 8.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.0, 46.3, 108.9 (dd, $J = 2.5, 2.6$ Hz), 111.2 (dd, $J = 3, 23$ Hz), 125.8 (dd, $J = 4, 19$ Hz), 127.5, 128.9, 129.1, 132.4 (dd, $J = 3.0, 7.0$ Hz), 137.7, 158.3 (dd, $J = 11, 247$ Hz), 159.91 (dd, $J = 11, 247$ Hz), 192.3 (t, $J = 3.0$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -107.2 (dd, $J = 6.8, 8.3$ Hz), -113.5 (dt, $J = 7.5, 8.3$ Hz); HRMS (EI-ion trap) m/z : $[\text{M} - 1]^+$ calcd for $\text{C}_{15}\text{H}_9\text{OSF}_2$, 275.0342; found 275.0345.

3.4.9. Synthesis of 6,8-Dichloro-2-phenylthiochroman-4-one (3La)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.08 mL, 0.225 mmol) and thiochromone (33.6 mg, 0.15 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, v/v), gave a light-yellow solid **3La** (35 mg, 76%): mp 112–113 °C; IR (neat) 3067 (w), 2921 (s), 1682 (s), 1571 (m), 1539 (w), 1453 (w), 1397 (s), 1283 (w), 1241 (m), 1177 (w), 1121 (w), 1051 (w), 808 (w), 767 (w), 697 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.00 (dd, $J = 3.2, 16.4$ Hz, 1 H), 3.10 (dd, $J = 13.2, 16.4$ Hz, 1 H), 4.45 (dd, $J = 3.2, 13.2$ Hz, 1 H), 7.15–7.45 (m, 5 H), 7.32 (d, $J = 2.4$ Hz, 1 H), 7.86 (d, $J = 2.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 44.8, 45.3, 127.51, 127.53, 128.9, 129.2, 131.0, 132.1, 132.5, 133.7, 137.5, 140.0, 192.6; HRMS (EI-ion trap) m/z : $[\text{M} - 1]^+$ calcd for $\text{C}_{15}\text{H}_9\text{OSCl}_2$, 306.9751; found 306.9765.

3.4.10. Synthesis of 8-Methoxy-2-phenylthiochroman-4-one (3Ma)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.16 mL, 0.44 mmol) and thiochromone (55 mg, 0.29 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, v/v), gave a light-yellow solid **3Ma** (66 mg, 84%): mp 147–148 °C; IR (neat) 3017 (w), 2972 (W), 2936 (w), 1673 (s), 1579 (m), 1559 (m), 1451 (m), 1420 (m), 1316 (m), 1254 (s), 1155 (w), 1055 (w), 1031 (s), 789 (m), 770 (m), 712 (w), 697 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.08 (dd, $J = 2.8, 16.0$ Hz, 1 H), 3.21 (dd, $J = 13.6, 16$ Hz, 1 H), 3.82 (s, 3 H), 4.54 (dd, $J = 2.8, 13.6$ Hz, 1 H), 6.91 (dd, $J = 1.2, 8.0$ Hz, 1 H), 7.09 (t, $J = 8.0$ Hz, 1 H), 7.22–7.32 (m, 3H), 7.33–7.38 (m, 2H), 7.71 (dd, $J = 1.2, 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 44.4, 46.0, 56.3, 114.2, 121.1, 124.8, 127.5, 128.5, 129.0, 131.3, 131.9, 138.7, 155.1, 194.6; HRMS (EI-ion trap) m/z : $[\text{M} + 1]^+$ calcd for $\text{C}_{16}\text{H}_{15}\text{O}_2\text{S}$, 271.0793; found 271.0794.

3.4.11. Synthesis of 2,3-Dihydro-2-phenyl-4H-naphtho[1,2-b]thiopyran-4-one (3Pa)

Employing General Procedure A, using phenylmagnesium bromide (2.8 M, 0.19 mL, 0.53 mmol) and thiochromone (75 mg, 0.354 mmol), after purification by flash column chromatography (silica gel, 0–2% ethyl acetate: hexanes, v/v), gave a light-yellow solid **3Pa** (82 mg, 80%): mp 144.0–145.0 °C; IR (neat) 3057 (w), 3031 (w), 2020 (w), 1668 (w), 1594 (m), 1552 (w), 1450 (w), 1326 (m), 1310 (m), 1267 (m), 1245 (m), 1165 (w), 1076 (w), 810 (m), 771 (m), 746 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.21 (dd, $J = 2.8, 16.4$ Hz, 1 H), 4.35 (dd, $J = 13.6, 16.4$ Hz, 1 H), 4.74 (dd, $J = 3.2, 13.6$ Hz, 1 H), 7.28–7.39 (m, 3H), 7.41–7.46 (m, 1H), 7.46–7.51 (m, 1H), 7.52–7.58 (m, 1H), 7.73–7.78 (m, 1H), 8.10–8.17 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 45.4, 45.8, 124.1, 125.1, 125.4, 126.8, 127.6, 127.7, 128.6, 128.7, 129.1, 129.2,

130.1, 135.5, 138.4, 142.9, 194.6; HRMS (EI-ion trap) m/z : $[M + 1]^+$ calcd for $C_{19}H_{15}OS$, 291.0844; found 291.0847.

3.4.12. Synthesis of 3-Chloro-2-(2-naphthyl)-4H-thiochromen-4-one (4Af)

To a dichloromethane (DCM) solution of 2-(2-naphthyl)thiochroman-4-one (1.0 equivalent, 0.542 mmol, 157.2 mg), NCS (*N*-chlorosuccinimide) (3.0 equivalent, 1.63 mmol, 217 mg) was added. The reaction mixture was stirred at room temperature overnight (12 h). It was then quenched with water (10 mL) and extracted with DCM (3×10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 . It was filtered and concentrated in vacuum. The crude product was purified by flash column chromatography (silica gel, 5% ethyl acetate: hexanes, *v/v*) to give **4Af** as a white solid (119 mg, 68%): mp 161.0–162.0 °C; IR (neat) 3052 (w), 2922 (w), 1621 (s), 1586 (s) 1562 (m), 1500 (w), 1462 (w), 1435 (w), 1320 (w), 1305 (w), 1272 (w), 1135 (w), 1112 (w), 851 (m), 839 (m), 735 (m) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.63 (m, 6 H), 7.82–7.88 (m, 2 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.96 (t, $J = 0.8$ Hz, 1 H), 8.57 (ddd, $J = 0.8, 1.6, 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.6, 125.9, 126.5, 127.0, 127.7, 127.9, 128.1, 128.5, 128.6, 128.7, 129.8, 130.5, 131.9, 132.6, 132.8, 133.7, 136.6, 148.4, 174.8; HRMS (EI-ion trap) m/z : $[M + 1]^+$ calcd for $C_{19}H_{12}OSCl$, 323.0297; found 323.0296.

3.4.13. Synthesis of 2-(4-Methoxyphenyl)thiochroman-4-one 1,1-dioxide (5Ac)

To a dry DCM solution of 2-(4-methoxyphenyl)thiochroman-4-one (94 mg, 0.348 mmol) under Ar atmosphere in a 50-mL RB flask, excess 3-meta-chloroperoxybenzoic acid (*m*-CPBA, 3.0 equivalent, 180 mg, 1.04 mmol) was added. The resultant mixture was stirred at room temperature until the reaction was complete by TLC monitoring (4–5 h). Then the reaction mixture was quenched with $NaHCO_3$ (10 mL) and diluted with DCM (10 mL). The organic layers were separated and the aqueous layer was extracted with DCM (2×10 mL). The organic layers were combined and washed with brine and dried over anhydrous Na_2SO_4 . It was filtered and concentrated in vacuum. The crude product was purified by flash column chromatography (silica gel, 20% ethyl acetate: hexanes, *v/v*) to give a white solid **5Ac** (78 mg, 74%): mp 163–164 °C; IR (neat) 3100 (w), 2902 (w), 1690 (s), 1587 (w), 1376 (m), 1312 (m), 1273 (s), 1150 (m), 1115 (s), 934 (m), 904 (m), 759 (m) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.41 (dd, $J = 3.2, 17.6$ Hz, 1 H), 3.85 (s, 3 H), 3.95 (dd, $J = 12.8, 17.6$ Hz, 1 H), 4.85 (dd, $J = 3.2, 12.8$ Hz, 1 H), 7.00 (dd, $J = 2, 6.8$ Hz, 1 H), 7.42 (dd, $J = 2, 6.8$ Hz, 2 H), 7.78 (td, $J = 1.2, 8$ Hz, 1 H), 7.85 (td, $J = 1.2, 8.0$ Hz, 1 H), 8.10 (dd, $J = 1.2, 8.0$ Hz, 1 H), 8.19 (dd, $J = 1.2, 8$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.2, 55.4, 63.5, 114.6, 119.7, 124.5, 128.7, 130.6, 131.1, 133.3, 135.1, 141.5, 160.9, 191.1; HRMS (EI-ion trap) m/z : $[M + 1]^+$ calcd for $C_{16}H_{15}O_4S$, 303.0691; found 303.0699.

3.4.14. Synthesis of 2-[3,5-(Trifluoromethyl)phenyl]thiochroman-4-one 1,1-dioxide (5Ae)

To a dry DCM solution of 2-[3,5-(trifluoromethyl)phenyl]thiochroman-4-one (116 mg, 0.308 mmol) under Ar atmosphere in a 50-mL RB flask, excess 3-meta-chloroperoxybenzoic acid (*m*CPBA, 3.0 equivalent, 0.924 mmol, 159 mg, *m*CPBA was 70–75%) was added. The resultant mixture was stirred at room temperature until the reaction was complete by TLC monitoring (4–5 h). Then, the reaction mixture was quenched with $NaHCO_3$ (10 mL) and diluted with DCM (10 mL). The organic layers were separated and the aqueous layer was extracted with DCM (2×10 mL). The organic layers were combined and washed with brine and dried over anhydrous Na_2SO_4 . It was filtered and concentrated in vacuum. The crude product was purified by flash column chromatography (silica gel, 20% ethyl acetate: hexanes, *v/v*) to give a white solid **5Ae** (88 mg, 70%): mp 162–163 °C; IR (neat) 3100 (w), 2902 (w), 1690 (s), 1627 (w), 1587 (w), 1469 (w), 1376 (m), 1313 (s), 1273 (s), 1199 (m), 1115 (s), 1038 (w), 934 (m), 904 (m), 844 (w), 780 (w), 759 (s), 706 (w), 679 (w) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.36 (dd, $J = 3.2, 17.6$ Hz, 1 H), 3.92 (dd, $J = 13.2, 17.6$ Hz, 1 H), 4.94 (dd, $J = 3.2, 12.8$ Hz, 1 H), 7.74 (dt, $J = 1.6, 7.6$ Hz, 1 H), 7.89 (s, 1 H), 7.93 (s, 1 H), 8.01 (dd, $J = 1.2, 8.0$ Hz, 1 H), 8.13 (dd, $J = 1.2, 8.0$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6, 63.1, 121.5, 122.8 (q, $J = 258$ Hz), 124.2, 124.5, 129.1, 130.0, (d, $J = 3$ Hz), 130.3,

130.7, 132.6 (q, $J = 34$ Hz), 133.9, 135.4, 140.7, 189.4; ^{19}F NMR (376 MHz, CDCl_3) $\delta -62.9$; HRMS (EI-ion trap) m/z : $[\text{M} + 1]^+$ calcd for $\text{C}_{17}\text{H}_{11}\text{O}_3\text{SF}_6$, 409.0333; found 409.0333.

3.4.15. Synthesis of 2-(2-Methylphenyl)thiochroman-4-ol (7Ab)

To a dry ethanol solution (3.0 mL) of 2-(2-methylphenyl)thiochroman-4-one (50 mg, 1.0 eq, 0.197 mmol, 50 mg) under argon, sodium borohydride (5 mg, 0.6 eq, 0.12 mmol, 10 mg) was added portion-wise. The resultant mixture was stirred at room temperature for 2 h when TLC monitoring showed that all the starting material was gone. Then solvent was evaporated, ice water (10 mL) was added, and the mixture was acidified with 10% HCl to pH = 1–2. It was then extracted with ethyl acetate (3×10 mL) and organic layers were combined, and washed with brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under vacuum to give the crude product. The crude product was then purified by flash column chromatography (silica gel, 10% ethyl acetate: hexanes, v/v) to give 2-(2-methylphenyl)thiochroman-4-ol **7Ab** as a white solid (41 mg, 81%): mp 146–147 °C; IR (neat) 3269 (sb), 3064 (w), 3021 (w), 2918 (s), 1953 (w), 1916 (w), 1590 (w), 1565 (w), 1487 (m), 1486 (s), 1435 (m), 1244 (w), 1220 (w), 1063 (m), 1021 (m), 753 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.0 (s, 1H), 2.47 (s, 3H), 2.48–2.53 (m, 1H), 2.67 (ddd, $J = 2.8, 5.2, 12.8$ Hz, 1 H), 4.86 (dd, $J = 3.2, 12$ Hz, 1 H), 5.0–5.10 (m, 1 H), 7.11–7.28 (m, 6H), 7.49–7.55 (m, 1 H), 7.65–7.73 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.3, 40.0, 40.3, 70.0, 124.8, 125.9, 126.7, 126.79, 126.80, 127.7, 127.8, 130.7, 134.1, 135.9, 136.6, 138.4; HRMS (EI-ion trap) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{ONaS}$, 279.0820; found 279.0826.

4. Conclusions

In conclusion, we successfully developed the conjugate addition of Grignard reagents to thiochromones catalyzed by $\text{CuCN} \cdot 2\text{LiCl}$ in the presence of chlorotrimethylsilane (TMSCl) as an activator to afford 2-alkylthiochroman-4-ones and thioflavanones (2-arylthiochroman-4-ones) in good yields. This reaction was shown to work well with a broad range of Grignard reagents, both alkyl and aromatic Grignard reagents. This synthetic approach will allow access to a broader scope of thiochromanones and thioflavanones due to the readily available Grignard reagents compared to organolithium reagents. Very interesting compounds, such as 6,8-difluorosubstituted thiochroman-4-ones, were synthesized for further studies. The 1,4-adducts, both 2-alkylthiochroman-4-ones and thioflavanones, can be utilized for additional synthetic applications and provide quick access that privileges sulfur-heterocycles.

Supplementary Materials: The following are available online.

Author Contributions: T.J.B., T.H., T.P.-F., N.A., S.H.W., M.L.C.T.Y.T., D.T.H., and N.D. performed the experiments. F.G. conceived and designed the experiments; F.G. wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NSF HBCU-UP RIA, grant number 1600987 and NSF EiR, grant number 1831339. Part of this research was funded NIH RISE, and grant number R25GM113774. Tania J. Bellinger, Nataleigh Austin, Mai Ling Yuk Tutein, and Nichele Deese are NIH RISE scholars. We like to thank NSF CUR-TP team (NSF, grant 1625354) for supporting the re-design of CH3236 (I&R) and the undergraduate transformation project. The APC was funded by NSF HBCU-UP RIA, grant number 1600987. We also like to thank Dr. Marcus Wright from Chemistry Department, Wake Forest University, Winston Salem for access to NMR facility and assistance in attaining NMR spectra. We thank WSSU Provost's Office for supporting the re-design of CH3236 (I&R). This is also part of the project that Mai Ling Tang Yuk Tutein, Ti'Bran Pickens-Flynn and Nataleigh Austin are working on for CH3236 (I&R) and CH4244 (Directed Research) courses, backward redesigned I&R and directed research, part of the NSF Council of Undergraduate Research Transformation Project.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are not available from the authors.



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