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Transition metal free intramolecular S-arylation: one-pot synthesis of thiochromen-4-ones

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ABSTRACT

A convenient one-pot method for the synthesis of thiochromen-4-ones by the condensation of 2′-haloacetophenone and dithioesters at room temperature in the presence of NaH in DMF in moderate to good yields has been developed. The method involves unusual intramolecular S-arylation. The reaction is operationally facile, readily scalable and offers rapid entry into substituted chromene-4-ones.

The thio-analog of naturally occurring flavones is 4*H*-thiochromen-4-one. Flavones and isoflavones, belong to an important class of natural products having a wide range of biological activities and pharmaceutical applications.[1a–d] Chromenes are widely present as key structural motifs in many natural products.[2a] Likewise the thiochromone dervatives exhibit antimalarial,[2b] antiviral, antibacterial,[2c] and antifungal activities,[3] besides their inhibitory effect of steroid sulfatase (STS)[4] and as specific inhibitors of ERK–MAP kinase signaling pathway[5] together with their applications in dyes for chemical fibers.[6] Moreover, 3-enynyl substituted thioflavones exhibit highly potent antitumor and anticarcinogenic effects[7a,b] whereas thiopyran and fused-thiopyran derivatives show antiinflammatory,[8a] antihyperplasia,[8b] antipsychotic,[8c] analgesic, and anticancer activities.[8d,e] Furthermore, the oxidized products of thiochromen-4-ones are used as the human cytomegalavirue protease inhibitors.[9] In addition, 4*H*-thiochromenoapomorphines have been found to possess a high dopamine receptor binding affinity.[10] Considering the biological and clinical importance of thioflavones, new synthetic strategies are being developed. Published reports revealed that the methods for the synthesis of thiochromones are limited and mainly involved in condensation of β-keto esters and thiophenols with polyphosphoric acid.[11]

Reportedly, β-(2-chloroaroyl) thioacetanilides are widely used as starting materials in three-component one-pot synthesis of fused tricyclic thiochromeno[2,3-*b*]pyridines, varying the other two reactants and conditions.[12] Cycloaddition of thiophthalic anhydride with alkynes is also reported.[13]

Recently, Muller and co-workers (2010) reported the synthesis of thiochromone derivatives from substituted *ortho*-haloaroyl chloride, alkynes, and sodium sulfide.[14] Although some approaches to the synthesis of 4*H*-thiochromen-4-one derivatives have been developed,[15] the methods often suffer from harsh reaction conditions, limited substrate scope and low yields. Dithioesters and oxodithioesters exhibit promising structural features as versatile intermediates in organic synthesis and their utility has been well recognized and reported recently.[16]

In continuation of our ongoing research interest for the synthesis of heterocycles via one-pot reaction,[17–23] and to devise a more general synthetic route for heterocycles, we explored the substituted thiochromones via heteroaromatic annulations of dithioesters with 2′-haloacetophenones. When 2′-haloacetophenone **1a** was treated with dithioesters **1b** in DMF in the presence of base NaH at room temperature, the corresponding thiochromone **1c** was obtained in 3–4 h in good yields (Scheme 1).

Optimization of the reaction conditions was done by screening various bases and solvents at room temperature. To start with, 2′-bromoacetophenone **1a** and phenyl dithioester **1b** were chosen as the model substrates. Establishing the effectiveness of the base, a reaction was performed only in DMF, which afforded no product even after 24 h (Table 1, entry 1) of stirring. Thus, the reaction was carried out with bases like K_2CO_3, KOH, *t*-BuONa, *t*-BuOK, and NaH, and the results are summarized in Table 1.

Next we optimized the loading of NaH; it was found that 1.5 equiv of NaH gave a maximum yield of 70% (Table 1, entry

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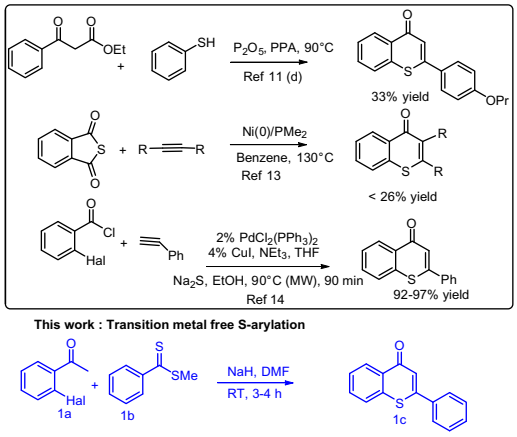


Scheme 1. Synthetic strategies for 4*H*-thiochromen-4-one.

Table 1
Optimization of one-pot synthesis of 4*H*-thiochromen-4-one

Entry	Base[a]	Solvent	Time (h)	Temp	Yield[b] (%)
1	—	DMF	24	Reflux	No product
2	K_2CO_3	DMF	24	Reflux	Trace
3	KOH	DMF	24	rt then reflux	Trace
4	*t*-BuONa	DMF	24	Reflux	5
5	*t*-BuONa	DMF	24	rt	10
6	*t*-BuOK	DMF	24	rt	15
7	*t*-BuOK	DMF	24	rt	20
8	NaH (1 equiv)	Et_2O	24	rt	No product
9	NaH (1 equiv)	*n*-Hexane	24	rt	10
10	NaH (1 equiv)	Benzene	24	rt	No product
11	NaH (1 equiv)	THF	24	rt	30
12	NaH (0.8 equiv)	DMF	16	rt	40
13	NaH (1.0 equiv)	DMF	12	rt	55
14	NaH (1.2 equiv)	DMF	10	rt	65
15	NaH (1.5 equiv)	DMF	3.5	rt	70
16	NaH (2.0 equiv)	DMF	3.0	rt	66
17	NaH (3.0 equiv)	DMF	2.5	rt	64

[a] The mixture of **1a** (1.0 mmol) and **1b** (1.0 mmol) was stirred in flask.
[b] Isolated yield.

15). Reducing the equivalents of NaH in the reaction not only increased the reaction time but also lowered the yield (Table 1, entries 13, 14). A higher yield was not achieved when NaH was increased to 2.0–3.0 equiv (Table 1, entries 16 and 17). While examining the effects of different solvents it was observed that DMF appeared to be the best choice for this transformation (Table 1, entry 15). Thus, the cleanest reaction with a simple work-up was achieved by employing 1.5 equiv of NaH in DMF at room temperature. Within 3–4 h the products were formed in moderate to good yields as bright yellow solids.[25]

Exploring the variability of this method it was expanded to methoxy- dimethoxy-, and trimethoxy phenyl–dithioester and thiophene–dithioester which transformed into corresponding thiochromen-4- ones in good yields (55–70%) (Table 2). To test the generality of this procedure, the reactions of different 2′-haloacetophenones with dithioesters were examined under optimized conditions (Table 2, **1c**–**10c**). The structures of all the 4*H*-thiochromen-4-ones were characterized by ^1H, ^{13}C NMR, and mass spectrometry (Scheme 2).

Interestingly, when halo-substituted reactant, like 2′,4′-dichloroacetophenone, was reacted with dithioesters, we observed thiochromen-4-ones in addition to substituted product in a S_NAr reaction of the chloro atom by the methylthio group,[24] (Table 3, **11c**–**14c**, **11d**–**14d**). This kindled our curiosity to check the preferable reactivity of halo-dithioesters with simple 2′-bromoace-

Table 2
Synthesized 4*H*-thiochromen-4-ones

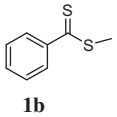
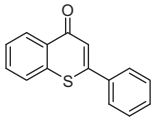
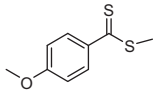
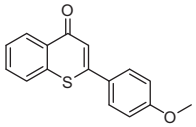
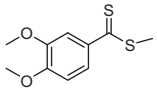
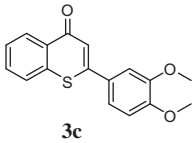
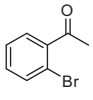
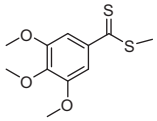
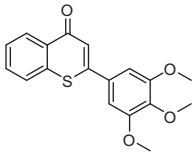
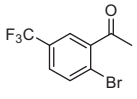
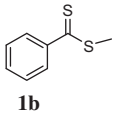
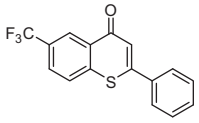
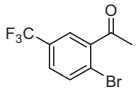
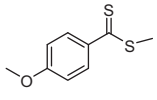
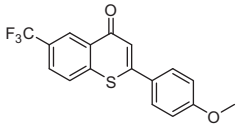
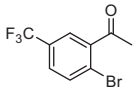
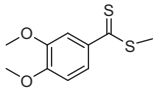
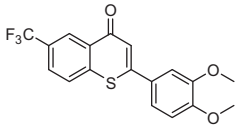
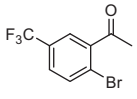
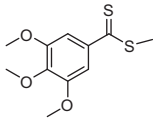
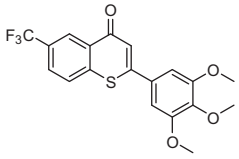
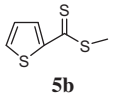
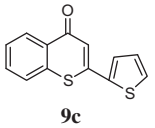
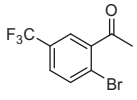
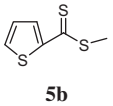
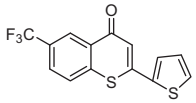
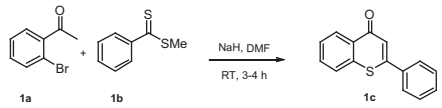
a	b	c[a]	Yield[b] (%)
 **1a**	 **1b**	 **1c**	64[c]
 **1a**	 **2b**	 **2c**	58[c]
 **1a**	 **3b**	 **3c**	78[c]
 **1a**	 **4b**	 **4c**	76[c]
 **2a**	 **1b**	 **5c**	63
 **2a**	 **2b**	 **6c**	65
 **2a**	 **3b**	 **7c**	66
 **2a**	 **4b**	 **8c**	79
 **1a**	 **5b**	 **9c**	55[c]

Table 2 (*continued*)

a	b	c[a]	Yield[b] (%)
 **2a**	 **5b**	 **10c**	63

[a] General conditions: **1a** (1.0 mmol), **1b** (1.0 mmol), NaH (1.5 mmol), in DMF, RT, 3-4 h.
[b] Isolated yield.
[c] Reported compounds.



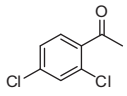
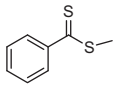
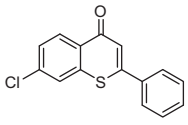
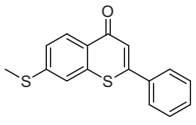
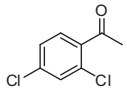
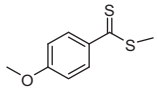
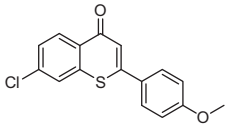
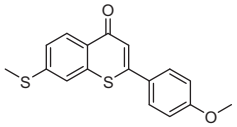
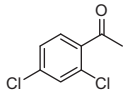
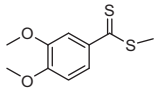
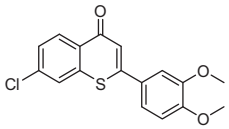
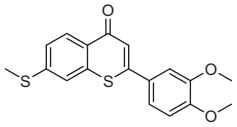
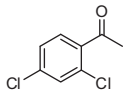
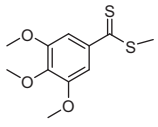
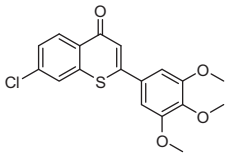
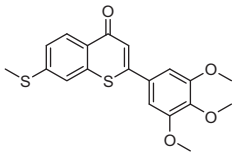
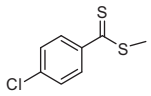
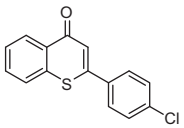
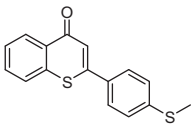
Scheme 2. Synthesized 4*H*-thiochromen-4-ones.

tophenone (Scheme 3) to form thiochromen-4-ones and methylthio products. The methylthio-substituted product was formed preferentially with flouro, then chloro followed by bromo-dithioesters, respectively, (Table 3, **15c**–**17c**, **15d**–**17d**). These were further verified by Mass, ^{1}H, and ^{13}C NMR analyses. The product formed with nitro-dithioester was found to be unstable and could not be characterized.

Mechanistically, the formation of 4*H*-thiochromene-4-one derivative is illustrated in Scheme 4. Reaction of 2′,4′-dichloroacetophenone **3a** with NaH in DMF provides carbanion intermediate **A**, which then reacts with dithioesters **1b** to afford 1,3-thioketone **B**. The 1,3-thioketone undergoes keto–enol tautomerization to generate **C**. Finally, an intramolecular nucleophlic S_NAr substitution occurs at o-halo position by the attack of the mercapto group leading to the formation of 4*H*-thiochromene-4-one **11c**, with the elimination of the alkyl halide group. Further, the chloro-derivative **11c** undergoes direct nucleophlic aryl substitution with sodium thiomethoxide to give **11d**.

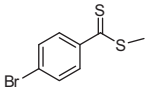
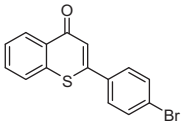
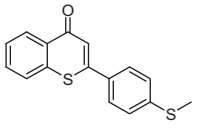
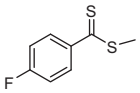
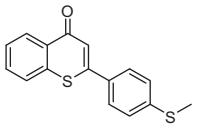
In summary, a general and efficient procedure for the synthesis of 4*H*-thiochromene-4-one derivatives has been established starting from 2′-haloacetophenone, dithioester, and NaH. The corresponding thioflavones have been produced in moderate to good yields. The intra-molecular Ullman-type S-arylation method does not need the aid of any transitional metal, and therefore avoids contamination of the products by toxic metals. This is an inexpensive and environmentally benign approach to synthesize thiochromone derivatives.

Table 3
Serendipitous methylthio-substituted 4*H*-thiochromene-4-one

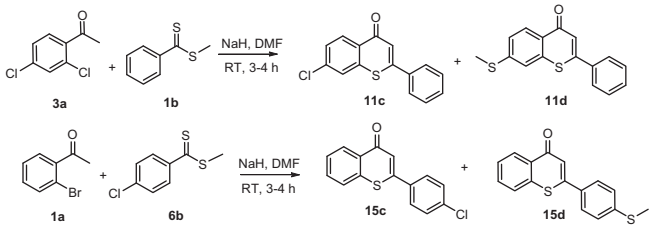
a	b	c[a]	d[a] yield[b] (%)
 **3a**	 **1b**	 **11c** **38%**	 **11d** **33%**
 **3a**	 **2b**	 **12c** **36%**	 **12d** **31%**
 **3a**	 **3b**	 **13c** **35%**	 **13d** **33%**
 **3a**	 **4b**	 **14c** **39%**	 **14d** **34%**
 **1a**	 **6b**	 **15c** **35%**	 **15d** **32%**

(*continued on next page*)

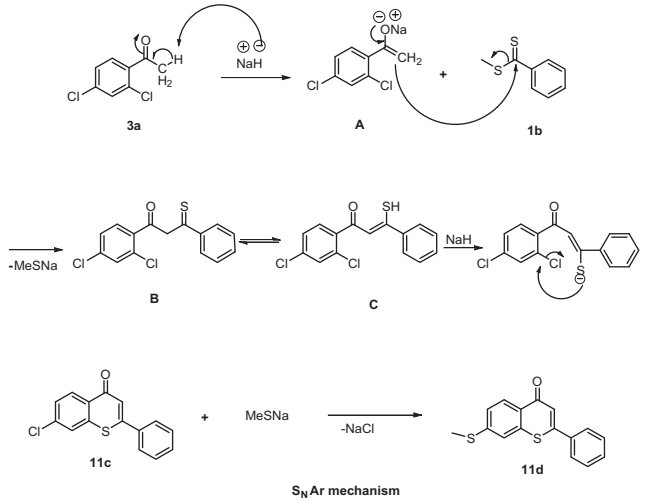
Table 3 (*continued*)

a	b	c[a]	d[a] yield[b] (%)
 **1a**	 **7b**	 **16c** **40%**	 **16d** **23%**
 **1a**	 **8b**	—[c]	 **17d** **50%**

[a] General conditions: **1a** (1.0 mmol), **1b** (1.0 mmol), NaH (1.5 mmol), in DMF, rt, 3–4 h.
[b] Isolated yield.
[c] Traces.



Scheme 3. A serendipitous result in case of halo-substituted reactants.



Scheme 4. A plausible mechanism for the synthesis of 4*H*-thiochromene-4-one derivatives.

Acknowledgments

The Ministry of Human Resource Development (MHRD) and University Grant Commission (UGC), New Delhi, India, are acknowledged for recognizing University of Mysore as the Institute of Excellence and for the financial assistance. We also thank Indian Institute of Science, Bangalore for spectral data.

Supplementary data

Supplementary data associated (general experimental details, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for all final products are available) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.094.

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25. *General procedure for one-pot synthesis of 4H-thiochromen-4-one 1-17c:* to a suspension of NaH (36 mg, 1.5 mmol) in DMF (1 mL) at 0 °C 2′-bromoacetophenone **1a** (197 mg, 1.0 mmol) was added followed by stirring for 10–15 min at room temperature. A solution of methyl benzodithioate **1b** (168 mg, 1.0 mmol) in DMF (2 mL) was added over a period of 10 min at 0 °C followed by stirring at room temperature for 3–4 h. The completion of reaction was monitored by TLC. The mixture was poured to water and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica using hexane/ethyl acetate (8:2) to afford thiochromene-4-ones; analytical data for some representative compounds: compound **1c**: cream color solid, yield 64%, mp 123–125 °C (lit. 126 °C)[1], ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, J_1 = 1 Hz, J_2 = 10 Hz, 1H), 7.69 (m, 2H), 7.66 (d, J = 1 Hz, 1H), 7.63 (t, J = 8.5 Hz, 2H), 7.55 (t, J = 3 Hz, 1H), 7.51 (m, 2H), 7.24 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.86, 153.02, 137.71, 136.61, 131.59, 130.88, 129.28, 128.54, 127.77, 126.99, 126.48, 123.48, IR (KBr): 3443, 1617, 1436, 1329,1098, 863, 759 cm^{-1}, MS (ESI + ion): m/z = 239.00 (M+1), Anal. Calcd for $C_{15}H_{10}OS$; C, 75.60; H, 4.23; Found: C, 75.56; H, 4.18; Compound **11d**: pale brown solid, yield 33%, mp 100–102 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, J = 8 Hz, 1H), 7.68 (m, 2H), 7.51 (m, 3H), 7.37 (m, 2H), 7.19 (s,1H), 2.57 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.43, 151.74, 145.60, 138.26, 136.17, 131.55, 129.94, 128.12, 127.16, 125.98, 123.13, 121.75, 14.42, IR (KBr): 3029, 2920, 1619, 1322, 825, 753 cm^{-1}, MS (ESI + ion): m/z = 285.0 (M+1), Anal. Calcd for $C_{16}H_{12}OS_2$; C, 67.57; H, 4.25; Found: C, 67.54; H, 4.22.