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Superelectrophilic Activation of Crotonic/Methacrylic Acids: Direct Access to Thiochroman-4-ones from Benzenethiols by Microwave-Assisted One-Pot Alkylation/Cyclic Acylation

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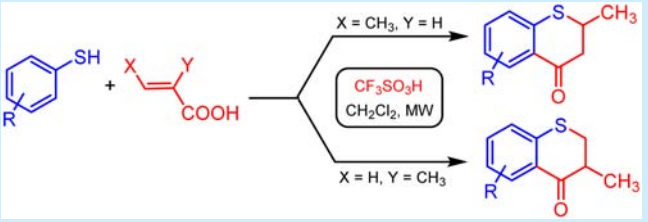
Supporting Information

ABSTRACT: An efficient microwave-assisted protocol for the synthesis of 2-/3-methylthiochroman-4-ones by superacid-catalyzed alkylation followed by cyclic acylation (cyclization via intramolecular acylation) is described. Using easily accessible benzenethiols and crotonic acid/methacrylic acid with triflic acid (as catalyst of choice for needed optimal acidity), the reaction was tuned toward the formation of the cyclized products in good selectivity and yield. A mechanism involving the formation of carbenium−carboxonium superelectrophilic species is suggested.



Thiochroman-4-ones have become valuable synthons and important precursors in organic synthesis. As reagents in heterocyclic synthesis, they have shown versatility and convenient application in many areas.[1] These compounds have also played vital roles in the synthesis of certain bioactive antiproliferative agents[2] as well as demonstrated direct bioactivity by themselves in the form of antifungal properties.[3−5] Recently, studies on the cytotoxic effect of a few thiochroman-4-one derivatives on tumor cells in vitro have been reported.[6] Results from such studies suggest that thiochromanone derivatives, such as (*Z*)-3-(chloromethylene)-6-fluorothiochroman-4-one, can kill tumor cells by inducing tumor cell apoptosis by increasing apoptosis-related factors.[7] Many substituted thiochromanones have been designated as effective "bioreductive alkylating agents" as demonstrated by compound B (Figure 1), an inhibitor of Ehrlich ascites tumor growth.[8] Therefore, investigation of the properties, synthetic routes, and applications of thiochroman-4-ones is steadily gaining much attention recently.

The thiochromanone family of heterocycles has not been studied as thoroughly as their oxygen counterparts, the chromanones, of which flavonones are a major subset. Thiochroman-4-ones have been prepared via several routes such as palladium-catalyzed carbonylative heteroannulation of iodothiophenols with allenes and carbon monoxide,[9] base-catalyzed cyclization of *β*-halopropanoic acids with arylthiophenols,[10−12] base-catalyzed condensation of *β*-propiolactone with 2-ethylthiophenol followed by acid-promoted cyclization,[13] and intramolecular Friedel−Crafts acylation with Lewis acids[14] as well as methanesulfonic acid.[15] To the best of our knowledge, there is no one-pot method for making these intriguing molecules directly from simple substrates such as thiophenols and crotonic/methacrylic acids. Thus, we were interested in designing a one-pot, superacid-catalyzed synthesis of thiochroman-4-ones from easily accessible and viable thio and keto precursor units—thiophenols and crotonic/methacrylic acids.

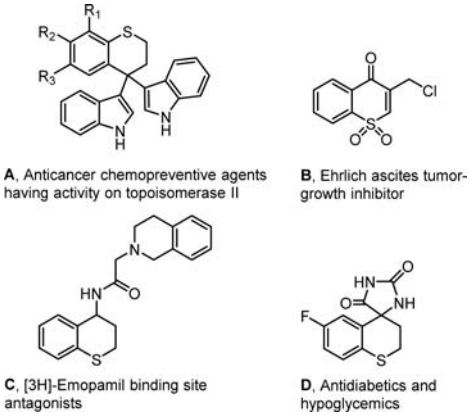


Figure 1. Some biologically active thiochromanone derivatives.

In our previous studies, we found that trifluoromethylated acrylic acids undergo superacidic activation in triflic acid, and their reaction with arenes under thermal conditions gave trifluoromethylated coumarins and indanones in good yields.[16]

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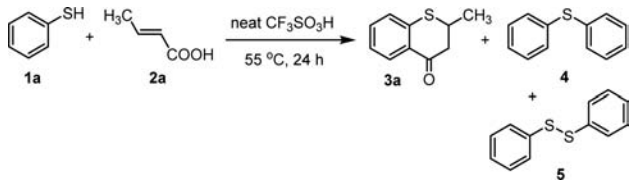
Therefore, initially, we conducted the triflic-acid-mediated condensation of crotonic acid (**2a**) with benzenethiol (**1a**) under thermal conditions (55 °C, 24 h) (Scheme 1).

Scheme 1. Reaction of Crotonic Acid with Benzenethiol



GC-MS analysis of the crude mixture after workup showed that the desired product 2-methylthiochroman-4-one **3a** did indeed form, but side products (diphenyl sulfide **4** and diphenyl disulfide **5**) had formed in significant amounts. The diphenyl sulfide was formed through an acid-mediated S_NAr reaction, while the disulfide was formed by air oxidation during the reaction or during the workup. This became clear when we found that the formation of the disulfide could be suppressed by performing the reaction under an inert (N_2) atmosphere. In our attempt to stop the formation of the sulfide, we thought that since the sulfide formation is kinetically rather slow, the side reaction could also be suppressed by using microwave irradiation and higher temperatures. Microwave heating has recently become very popular in organic synthesis, and several reviews have been published.[17]

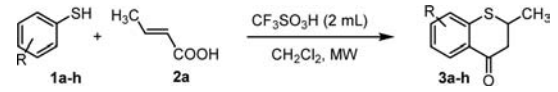
To our delight, the desired 2-methylthiochroman-4-one **3a** was easily obtained in pure form after column chromatography. It should be noted that the microwave-promoted reaction was *cleaner* than the corresponding thermal reaction (the separation by SiO_2 flash column chromatography was much easier due to a significant decrease in side products). The yield was further improved by using dry dichloromethane as a cosolvent. Using this protocol, a series of benzenethiols was reacted with crotonic acid (Table 1) to afford the corresponding 2-methylthiochroman-4-ones.

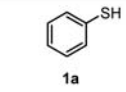
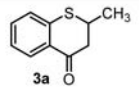
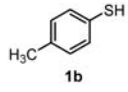
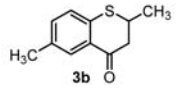
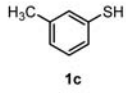
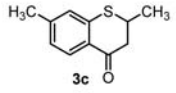
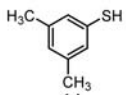
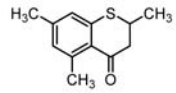
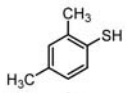
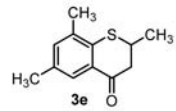
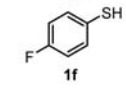
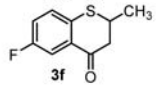
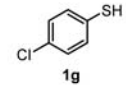
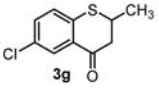
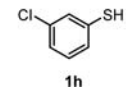
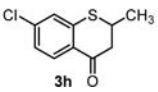
The reactions of the various benzenethiols with crotonic acid proceeded cleanly, with few side products (SiO_2 flash column purification involved separation of unreacted thiol or minor amounts of disulfide from the product). Activated aromatic rings generally gave higher yields, and the presence of a *para* directing group *para* to the site of acylation improved the yield of product further. However, with more deactivating substituents (such as −Br and $-NO_2$), the reaction was found to be sluggish and the product could not be formed cleanly. Interestingly, in contrast to our expectation, 2,4-dimethylbenezenethiol **1e** only gave the desired product in 40% yield; substitution *ortho* to the sulfur was not well tolerated, likely due to steric or unfavorable electronic factors (the site of acylation is *meta* to both methyl groups).

2-Thionaphthol **1j** proved too reactive (GC-MS analysis of the crude revealed a very complex mixture of products), and 4-methoxythiophenol **1i** yielded an intractable solid that was insoluble in common solvents. 4-Aminothiophenol also failed to give any product, probably due to the highly deactivating nature of the ammonium group (in the highly acidic medium, $-NH_2$ is completely protonated to $-NH_3^+$).

When 4-hydroxythiophenol was used as a substrate, cyclization failed to take place, and instead, the thioester was obtained as the major product. When the reaction was conducted in weaker acids (CF_3COOH, CH_3SO_3H), GC analysis of the crude reaction mixtures revealed poor conversion (<5%) of the starting materials. In CF_3COOH medium, the major product observed (by GC analysis) was the trifluoroacetyl thioester.

Table 1. Synthesis of 2-Methylthiochroman-4-ones[a]



entry	substrate	product	conditions	yield (%)
1	 1a	 3a	125 °C, 5 min	70
2	 1b	 3b	125 °C, 5 min	73
3	 1c	 3c	125 °C, 5 min	81
4	 1d	 3d	125 °C, 5 min	78
5	 1e	 3e	125 °C, 5 min	40
6	 1f	 3f	135 °C, 5 min	64
7	 1g	 3g	155 °C, 5 min	54
8	 1h	 3h	145 °C, 5 min	61

[a]Reactions were carried out with crotonic acid **2a** (2 mmol) and thiophenol (2 mmol) in dry CH_2Cl_2 (1 mL) and CF_3SO_3H (2 mL).

This methodology was also extended to methacrylic acid **2b** for the synthesis of 3-methylthiochroman-4-ones **6a**−**h**′ (Table 2). In the case of methacrylic acid **2b**, the reactions were carried out using commercially available dry CH_2Cl_2 but did not require inert conditions.

A probable mechanism is proposed as follows. Initial protonation of the crotonic acid by triflic acid gives the carboxonium ion **7**. Further protosolvation by the superacidic medium results in a small equilibrium amount of the carbenium−carboxonium superelectrophile **8**, which is immediately quenched by the nucleophilic attack of sulfur of thiophenol, forming **9** and subsequently the carboxonium ion **10**. This then undergoes intramolecular Friedel−Crafts acylation, resulting in the ring closure to yield the thiochroman-4-one product **3a**. Reaction of methacrylic acid also can be explained as following a similar mechanistic pathway.

It is quite evident from the product that the alkylation step occurs first rather than the acylation driving the acylation to occur *ortho* to the thio functionality (acylation is generally extremely regioselective for the *para* position when conducted with *o*/*p* directing substituents). In addition, when 3,5-bis(trifluoromethyl)benzenethiol was used as a substrate, no cyclization product was obtained. Instead, both ^{19}F and ^{1}H NMR support the formation of the corresponding arylpropanoic acid. This suggests that the benzene ring with the two CF_3 groups is

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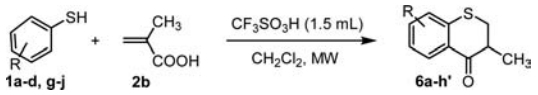
Table 2. Synthesis of 3-Methylthiochroman-4-ones[a]



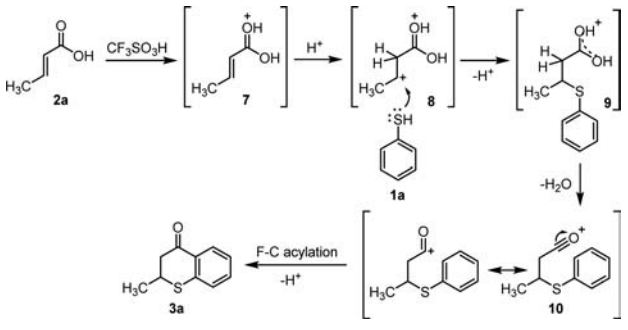
entry	substrate	product	conditions	yield (%)
1	1a	6a	110 °C, 5 min	96
2	1b	6b	110 °C, 5 min	66
3	1c	6c	110°C, 5 min	99
4	1d	6d	110 °C, 5 min	97
5	1g	6e	110 °C, 5 min	72
6	1h	6f	110 °C, 5 min	99
7	1i	6g	110 °C, 5 min	94
8	1j	6h + 6h'	110 °C, 5 min	22

[a]Reactions were carried out with methacrylic acid **2a** (1.18 mmol) and thiophenol (1.18 mmol) in CH_2Cl_2 (0.5 mL) and CF_3SO_3H (1.5 mL).

too deactivated to participate in a Friedel–Crafts acylation. Formation of the carbenium–carboxonium dication **8** is a crucial step, which is possible under the superacidic condition provided by triflic acid (Scheme 2).[18]

In summary, we have developed an efficient direct route to both 2- and 3-methylthiochroman-4-ones (**3** and **6**) via superacid-catalyzed sequential alkylation/cyclic acylation. Benzenethiols with both electron-donating and electron-withdrawing groups are tolerated, affording the desired products in moderate to high yields in most cases.

Scheme 2. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03172.

Experimental procedures and full characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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