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Synthesis of Thiochromans via [3+3] Annulation of Aminocyclopropanes with Thiophenols

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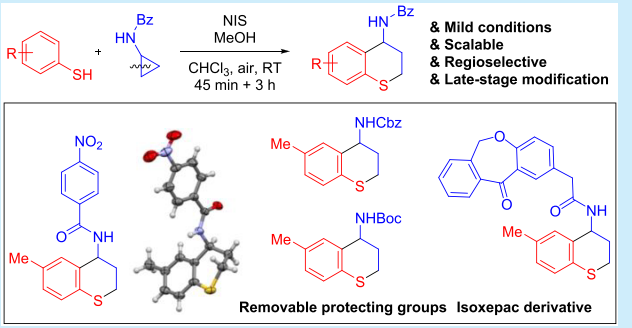
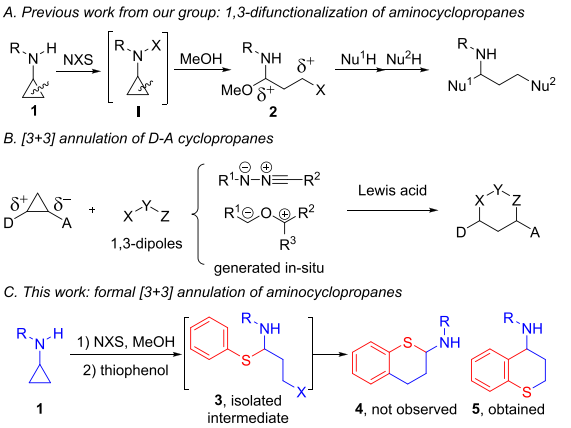
ABSTRACT: We report the one-pot synthesis of 4-amino thiochromans using simple aminocyclopropanes and thiophenols through a formal [3+3] annulation reaction. This reaction proceeds under mild conditions with good functional group tolerance. The thiochroman core was formed with complete regioselectivity, and modification of complex drug molecules containing an aminocyclopropane was also realized.



Aminocyclopropanes are important building blocks in organic chemistry.[1] While donor−acceptor cyclopropanes with amino groups as donors (D−A aminocyclopropanes) have attracted an enormous amount of attention in recent years from organic chemists and much progress has been achieved,[2] simple aminocyclopropanes lacking electron-withdrawing groups at the β position are relatively less studied for ring-opening transformations. Current methodologies mainly focused on transition metal catalysis[3] or photoredox/electrocatalysis[4] to activate either the C−C bond or the amino group. In 2019, inspired by recent progress in the Hofmann−Löffler−Freytag (HLF) reaction,[5] our group reported a metal-free method for the activation of simple aminocyclopropanes **1** via halogenated intermediate **I**.[6] The synthetic equivalent of a 1,3-biscationic synthon was obtained in the form of 3-halogenated N,O-acetals **2** after reaction with methanol (Scheme 1A). Linear 1,3-difunctionalized amines were synthesized by adding two nucleophiles sequentially to crude **2**. Inspired by recent examples of [3+3] annulations using donor−acceptor cyclopropanes as 1,3-zwitterionic synthons for annulation with 1,3-dipoles (Scheme 1B),[7] we wondered if the biscationic synthons developed by our group could be exploited for annulation reactions with bis-nucleophiles. During our investigation of the reaction of these synthons with nucleophiles, we observed the formation of thiochroman products with thiophenol (Scheme 1C). On the basis of the favored reaction of nucleophiles at the acetal position, we expected the formation of 2-amino thiochroman **4** via N,S-acetal **3**. However, two-dimensional NMR spectra indicated that 4-amino thiochroman **5** had been formed. This nonclassical regioselectivity attracted our interest and motivated us to investigate the scope of this new type of [3+3] annulation as well as the reaction mechanism.

Scheme 1. Oxidative Difunctionalization of Aminocyclopropanes and [3+3] Annulations



Herein, we report the result of these studies leading to a highly regioselective [3+3] annulation reaction to yield 4-amino thiochromans. Although thiochroman and its derivatives have exhibited biological activities,[8] efficient methods for the construction of the thiochroman core remain rare.[9] To the best of our knowledge, there are only two reports disclosing [3+3] annulations for the efficient synthesis of thiochromans from

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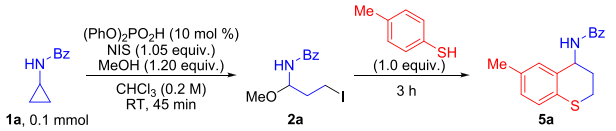
thiophenols. In 2018, Pullarkat and co-workers realized a triflic acid-catalyzed tandem allylic substitution−cyclization reaction for the synthesis of 1,4-disubstituted thiochromans.[10] A high reaction temperature was necessary to force ring closure. More recently, Namboothiri and co-workers reported the synthesis of thiochromans by using indoline-2-thione as the starting material.[11] It is therefore of high interest to develop a [3+3] formal annulation between simple aminocyclopropanes and thiophenols for accessing 4-amino thiochromans.

On the basis of our preliminary result, we chose *N*-cyclopropylbenzamide **1a** as the starting material for the preparation of biscationic synthon intermediate **2a** by reaction with NIS under acidic conditions in chloroform (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from the standard condition	yield[b] (%)
1	none	79
2	DCM as solvent	78
3	MeCN as solvent	48
4	without $(PhO)_2PO_2H$	70
5	adding thiophenol at the beginning	10
6	NBS instead of NIS	38[c]

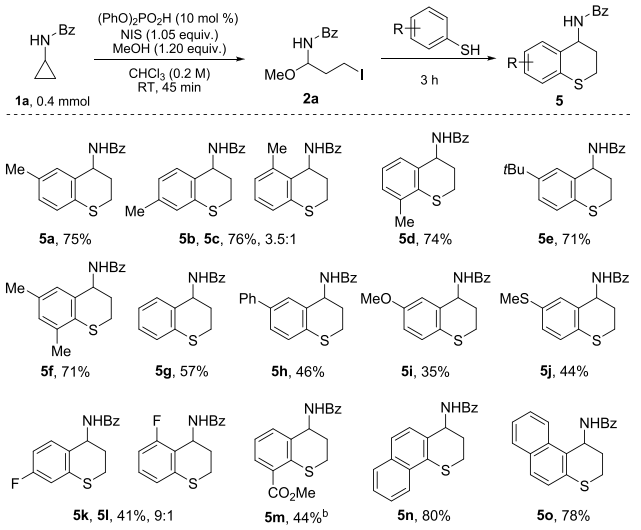
[a]Reactions were performed at room temperature under air for the indicated time. [b]The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard. [c]The reaction mixture was stirred for 3 h in the first step.

After formation of **2a**, 4-methylbenzenethiol was added to the reaction mixture and a good yield of **5a** was obtained (entry 1). Running the reaction in other solvents like dichloromethane or acetonitrile was also possible (entry 2 or 3, respectively). The reaction took place even in the absence of diphenyl phosphate, giving **5a** in 70% yield after the same reaction time (entry 4). However, adding 4-methylbenzenethiol at the beginning of the reaction gave a low yield, probably due to decomposition of thiophenol mediated by NIS (entry 5). With NBS as the electrophile instead of NIS, the first step was efficient, but only 38% of **5a** was formed during the second step (entry 6).

With the optimal conditions in hand, we then examined the scope of thiophenols (Scheme 2). A series of thiophenols with a methyl substituent at the *para*, *meta*, and *ortho* positions gave the corresponding thiochromans **5a−d** with a methyl group at positions 6, 7(5), and 8, respectively, in good yields. With 4-*tert*-butyl- or 2,4-dimethyl-substituted thiophenols, **5e** and **5f** were obtained in 71% yield. A slightly lower yield was observed for **5g** when using unsubstituted thiophenol as the reaction partner. With a phenyl- or electron-donating substituent like a methoxy or a methylthio group at the *para* position, products **5h−j** were obtained in yields ranging from 35% to 46%. Electron poor thiophenols like 3-fluorothiophenol or methyl 2-mercaptobenzoate were also tolerated, affording products **5k**/**5l** and **5m** in 41% and 44% yields, respectively. Naphthalene-1-thiol and naphthalene-2-thiol gave the corresponding products **5n** and **5o** in 80% and 78% yields, respectively.

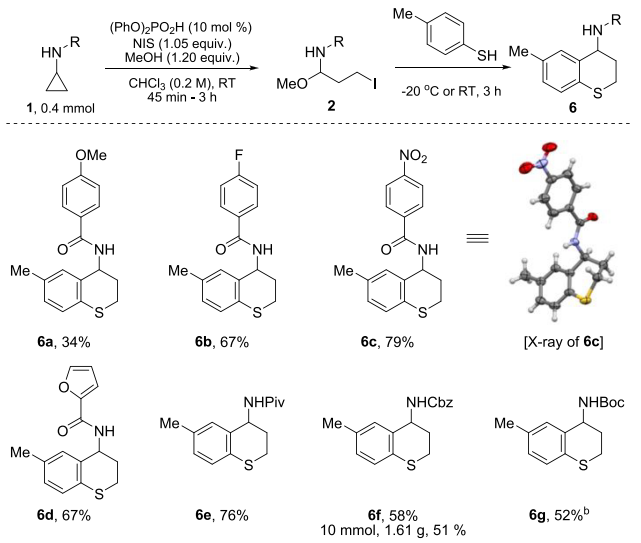
We then explored the reaction scope for aminocyclopropanes with different protecting groups (Scheme 3). With electron-donating substituents such as a 4-methoxy group on

Scheme 2. Scope of Thiophenols[a]



[a]Reactions were performed at a 0.4 mmol scale for the indicated time unless otherwise noted. [b]The reaction mixture was stirred for 20 h in the second step.

Scheme 3. Scope of Aminocyclopropanes[a]



[a]Reactions were performed at a 0.4 mmol scale for the indicated time. [b]The second step was carried out at −20 °C.

the benzene ring, product **6a** was isolated in a low yield, possibly due to polymerization of the intermediate. With electron-withdrawing groups on the benzene ring like 4-fluoro or 4-nitro, products **6b** and **6c** were formed in 67% and 79% yields, respectively. The structure of **6c** was confirmed by X-ray diffraction.[12] A 2-furoyl group on the aminocyclopropane was well tolerated, giving product **6d** in 67% yield. With a pivalate protecting group, product **6e** was isolated in 76% yield. Carbamate-substituted cyclopropanes can also undergo this transformation, giving desired products **6f** and **6g** in 58% and 52% yields, respectively. The synthesis of **6f** was scaled up to 10 mmol, and 1.61 g (51% yield) of **6f** was obtained.

The amide-substituted cyclopropanes needed for the annulation can be easily accessed by standard amide bond formation between a carboxylic acid and commercial amino-cyclopropane. Therefore, the [3+3] annulation can be used for

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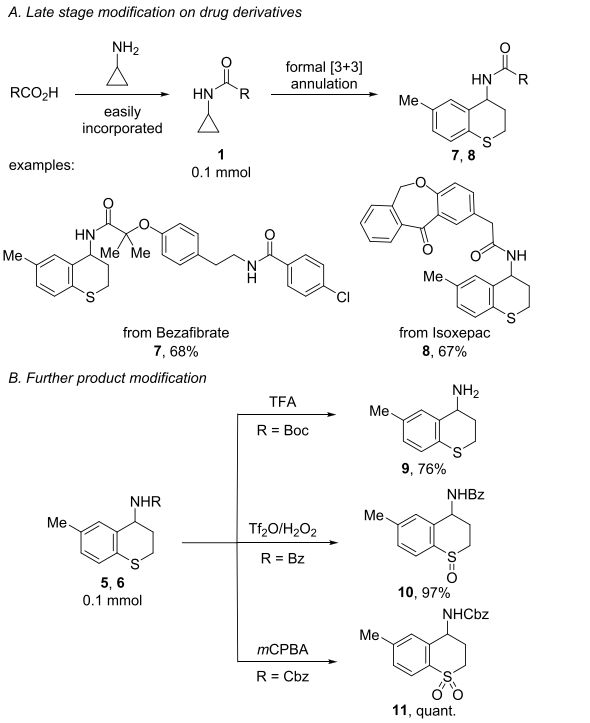
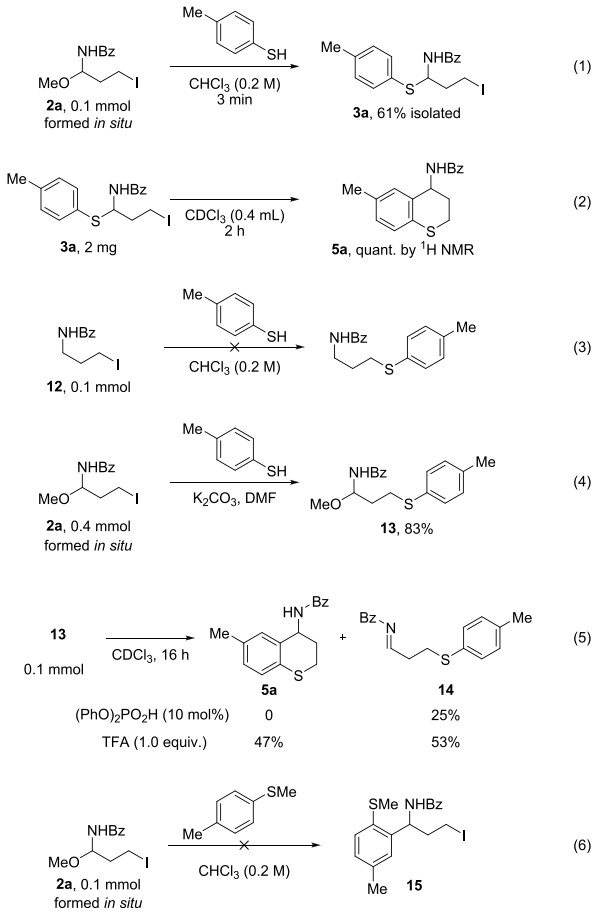
the late-stage modification of drugs containing carboxylic acids. This strategy was applied to the lipid-lowering agent bezafibrate and the anti-inflammatory drug isoxepac: thiochroman products **7** and **8** were formed in 68% and 67% yields, respectively (Scheme 4A).

Scheme 4. Late-Stage Modification and Functionalization of the Products



Scheme 5. Experiments for the Elucidation of the Reaction Mechanism

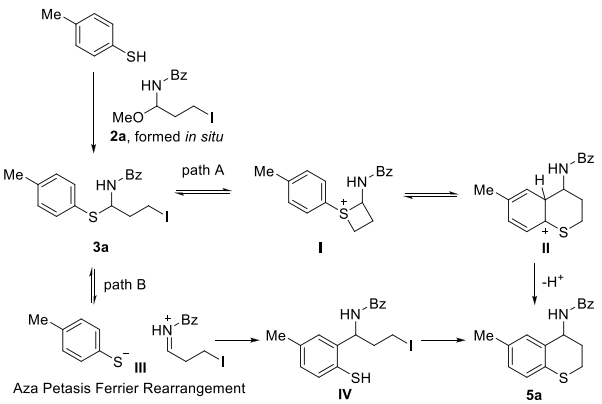


To highlight the synthetic utility of our 4-amino thiochroman products, a series of transformations were performed (Scheme 4B). With Boc as the protecting group, free amine **9** was easily obtained from **6g** in 76% yield. The thiochroman product can also be oxidized to sulfoxide **10** (97% yield from **5a**) or sulfone **11** (quantitative yield from **6f**). It is important to note that 4-amino thiochroman derivatives were reported to be potent aldose reductase inhibitors[13] or sirtuin 5 (SIRT5) inhibitors.[14] They were also reported to have excellent selective antagonistic activity on an α_{1D} adrenergic receptor.[15]

The unexpected formation of 4-amino thiochromans motivated us to perform a series of experiments to gain some insight into the mechanism. By performing the standard reaction in $CDCl_3$ and following the progress of the reaction by ^1H NMR, we observed the conversion of **2a** into a first intermediate, which was isolated in 61% yield and was identified as N,S-acetal **3a** after purification by column chromatography (Scheme 5, eq 1). The transformation from **3a** to thiochroman **5a** was spontaneous in $CDCl_3$ and was complete in 2 h, indicating the formation of N,S-acetal **3a** is not off-cycle (eq 2). An unknown intermediate, which can be stabilized by adding excess K_2CO_3 to the solution, was observed by ^1H NMR during the transformation from **3a** to **5a**. However, attempts to isolate this intermediate failed as it was formed only in a small ratio (see the Supporting Information for details). **2a** was then reduced to give alkyl iodide **12**. No reaction was observed between 4-methylbenzenethiol and **12** under neutral or acidic conditions (eq 3). Indeed, the S_N2 reaction took place efficiently only under basic conditions (eq 4) and conversion of isolated product **13** into thiochroman product **5a** was not very efficient even in the presence of 1.0 equiv of TFA for 16 h, as it was accompanied by the formation of imine intermediate **14** (eq 5). When **2a** was mixed with methyl *p*-tolyl sulfide, no product **15** resulting from an intermolecular Friedel–Crafts reaction was observed (eq 6).

On the basis of these experiments, we propose a speculative mechanism (Scheme 6). Once 4-methylbenzenethiol was added, N,S-acetal **3a** was formed as the first intermediate. Due to the nucleophilicity of the sulfur atom, an intramolecular

Scheme 6. Proposed Speculative Reaction Mechanism



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S_N2 reaction would take place to form sulfonium salt **I**, which may be the unknown intermediate observed from ^1H NMR experiments (path A). The following steps involving ring opening of the four-membered ring, intramolecular Friedel–Crafts reaction, and deprotonation of **II** should be fast, as no other intermediates were observed from ^1H NMR experiments. A mechanism involving a 1,3-shift can be considered, as imine **14** was not observed. Another way to explain the migration of the sulfur atom from the N,S-acetal carbon atom to the terminal carbon atom would involve an aza-Petasis Ferrier rearrangement[16] via ion pair **III** to give **IV**, followed by an intramolecular S_N2 reaction (path B). Nevertheless, path A seems to be more reasonable, considering the stability of the unknown intermediate in the presence of K_2CO_3, which would be expected to accelerate an S_N2 process.

In summary, we have developed an efficient and regioselective [3+3] annulation for the synthesis of 4-amino thiochromans. Good functional group tolerance was observed for electron-donating and electron-withdrawing substituents on both thiophenols and aminocyclopropanes. Late-stage modification of drug derivatives containing an aminocyclopropane was successful, and deprotection of the amino group was demonstrated. An enantioselective synthesis as well as other annulations involving dielectrophilic synthons derived from aminocyclopropanes is under investigation in our group and will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03528.

Experimental details and general procedures for the synthesis of 4-amino thiochromans, scale-up of the reaction, product modification, mechanistic studies, compound characterization methods and data, and spectra (PDF)

Accession Codes

CCDC 2034409 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.
Raw NMR, MS, and IR data are available at zenodo.org (DOI: 10.5281/zenodo.4194211).

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