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Metal- and Catalyst-Free One-Pot Cascade Coupling of α-Enolic Dithioesters with in situ Generated 4-Chloro-3-formylcoumarin: Access to Thioxothiopyrano[3,2-*c*]chromen-5(2*H*)-ones

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Abstract. An efficient and viable one-pot protocol for the synthesis of a specific class of 2-thioxothiopyrano[3,2-*c*] chromen-5(2*H*)-ones has been devised by the cross-coupling of 4-hydroxycoumarin and α-enolic dithioesters under metal- and additive-free conditions in open air. The reaction proceeds via *in situ* generation of 4-chloro-3-formylcoumarin followed by consecutive Michael-type addition/intramolecular cyclization/ elimination cascade, enabling the creation of thiopyran-2-thione ring over coumarin framework through successive formation of C–C and C–S bonds. Remarkably, the benign conditions, atom-economy, and quantifying forbearance of a wide horizon of functional groups are added characteristics to this strategy.

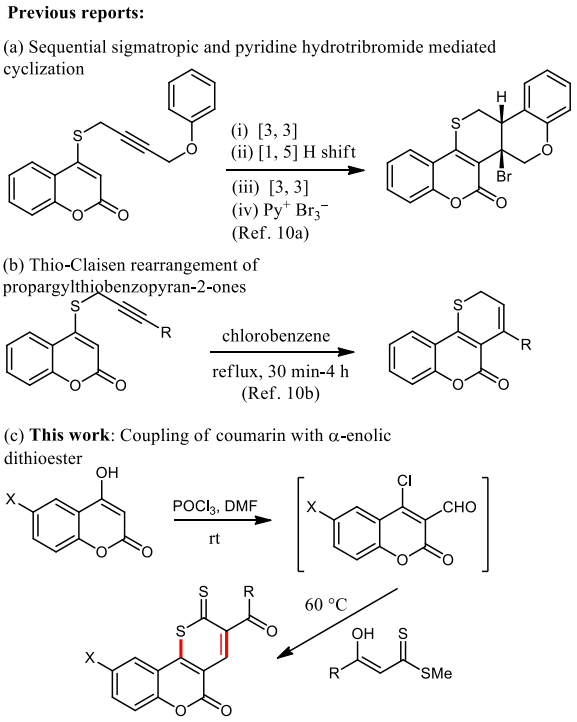
Keywords: α-Enolic dithioesters; Coumarin; 4-Chloro-3-formylcoumarin; Heteroannulation; Thiopyran annulated coumarin

Substituted/annulated coumarins are important synthetic targets for both the pharmaceutical industries and academic laboratories. They have always fascinated synthetic and medicinal chemists because of their comprehensive pharmacological profiles such as antiallergic, antibiotic, anticancerous, antitumor, antidiabetic, anticoagulant, antioxidant and antihypertensive properties.[1-3] Addition of heterocyclic moiety to coumarin nucleus enhances its biological applications and therapeutic values.[4] Coumarin fused heterocycles are present as core structures in many natural products and biologically active molecules such as alkaloids, tocopherols, and flavonoids.[5] Pyrano-fused coumarins have been explored for various biological properties like antihypertensive, spasmolytic, and activity towards potential cancer cells.[6] Furthermore, many of the coumarin derivatives also found application as insecticides[7a] and biodegradable chemicals[7b-g] for agricultural industries. In addition to medicinal applications, molecules bearing coumarin moiety have been used as fluorescent probes for biothiols.[8] The present popularity of the modified annulated coumarin derivatives is mainly due to their close structural relationship to some clinically important molecules, which could open the door to many challenges both in the areas of synthetic organic and medicinal chemistry. Therefore, much attention has been paid towards the synthesis of substituted/annulated coumarins.[9]

In spite of a wide range of literature reports towards the synthesis of coumarin derivatives, it is still highly desirable to explore operationally simple, efficient and widely applicable approach to the synthesis of annulated coumarins. Thiopyrano-fused coumarins have been synthesized via sigmatropic rearrangement[10a] and thio Claisen-type rearrangement.[10b] To the best of our knowledge, no report on the synthesis of 2-thioxothiopyrano fused coumarins utilizing α-enolic dithioesters is known to date (Scheme 1). For the success of any protocol, the choice of substrate and reagent is highly vital and dominant factor. The inherent synthetic tunability of substrates makes them highly attractive in synthesis. One such simple molecule is α-enolic dithioester, which bears both nucleophilic and electrophilic centers. α-Enolic dithioesters have become without doubt one of the most exciting and popular species in organic synthesis due to the ease of their preparation and modularity in stereoelectronic properties.

Over the past decade, α-enolic dithioesters having multiple reactive centers not only received considerable attention of synthetic chemists, but also have been extensively exploited for the construction of diverse heterocyclic scaffolds.[11] Inspired by exceptional reactivity and in line with our long-standing interest to construct diverse heterocyclic frameworks employing α-enolic dithioesters as a key substrate,[12] we intended to react α-enolic dithioester with coumarin derivative with a vision to get annulated coumarin framework. Herein, we report a one-pot domino approach to assemble thioxopyrano

annulated coumarin derivatives from α-enolic dithioester under metal- and additive-free conditions in open air (Scheme 1c).



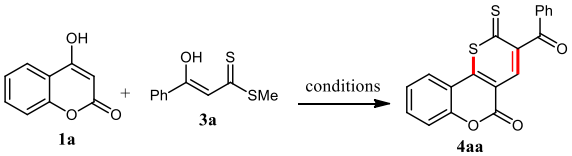
Scheme 1. Strategy for the synthesis of annulated coumarins.

To this end, to establish the viability of our new concise approach, we intensively investigated the model reaction of coumarin (**1a**) with methyl-3-hydroxy-3-phenyl-prop-2-enedithioate (**3a**) in $POCl_3$-DMF mixture in open air, and the results are listed in Table 1. Initially, we performed the test reaction of 1a (0.25 mmol) in $POCl_3$-DMF mixture (1:6 equiv.) at 0 °C for 30 minutes, followed by slow addition of dithioester **3a** (0.25 mmol) at room temperature. No trace of the product was obtained even after 24 h of stirring, and the substrates **1a** and **3a** remained completely unconsumed (Table 1, entry 1). To check the effect of temperature on the reaction, the test reaction was carried out at higher temperatures (Table 1, entries 2-4). It has been observed that maximum conversion occurred at 60 °C, providing the desired product **4aa** in 42% yield within 8 h (Table 1, entry 3). Further higher temperature (80 °C) made the reaction messy, and reduced the yield of product **4aa** to 30% (Table 1, entry 4).

To improve the efficiency of the reaction, next we assessed the amount of $POCl_3$ at 60 °C (Table 1, entries 5-8). It was found that 6 equiv. of $POCl_3$ drives the reaction smoothly furnishing the desired product 4aa in 77% yield within 6 h (Table 1, entry 7). Further increase in the amount of $POCl_3$ (8 equiv.) could not improve the result (Table 1, entry 8). Next, we surveyed the amount of DMF. Lowering the amount of DMF from 6 equivalents, decreased the yield of the product, and increasing the amount of DMF could not provide better result (Table 1, entries 9 and 10). Thus, the optimum condition for the reaction was achieved by employing **1a** (0.25 mmol), **3a** (0.25 mmol), $POCl_3$-DMF mixture (6:6 equiv.) at 60 °C in open air (Table 1, entry 7).

With the established optimal conditions in hand (Table 1, entry 7), we then set out to explore the scope of this novel coupling reaction by allowing a variety of structurally diverse α-enolic dithioesters bearing aryl, hetaryl, and extended aromatic substituents at R moiety, and the results are summarized in table 2. The influence of substituents in the phenyl ring (R moiety) of α-enolic dithioesters **3** was first investigated. The variants of the substituents did not hamper the reaction process, and proved to be the suitable substrates for this protocol to access diverse thiopyran fused coumarin derivatives **4** in good yields. The diverse substituents like -OMe, -Me, -Et, -Cl, $-CF_3$, -F and $-OCH_2O$- groups regardless of their substitution patterns (*ortho*, *meta*, *para*) on the phenyl ring (R moiety) were found to be well-suited under the optimal reaction conditions affording the corresponding products in high yields (Table 2, **4ab-4al**), revealing no obvious electronic and steric impact from the substituents. The introduction of halogen moiety into target product is attractive because of their potential towards cross-coupling for further synthetic elaborations.

Table 1. Optimization of reaction conditions.[a]



Entry	Reagent	Temp (°C)	Time (h)	Yield[b] (%)
1	$POCl_3$-DMF (1:6)	rt	24	NR
2	$POCl_3$-DMF (1:6)	40	8	20
3	$POCl_3$-DMF (1:6)	60	8	42
4	$POCl_3$-DMF (1:6)	80	8	30
5	$POCl_3$-DMF (2:6)	60	6	48
6	$POCl_3$-DMF (4:6)	60	6	62
7	$POCl_3$-DMF (6:6)	60	6	77
8	$POCl_3$-DMF (8:6)	60	6	77
9	$POCl_3$-DMF (6:4)	60	6	66
10	$POCl_3$-DMF (6:8)	60	6	77

[a] Reaction conditions: **1a** (0.25 mmol), **3a** (0.25 mmol) in open air. [b] Isolated yield. NR = No reaction reaction

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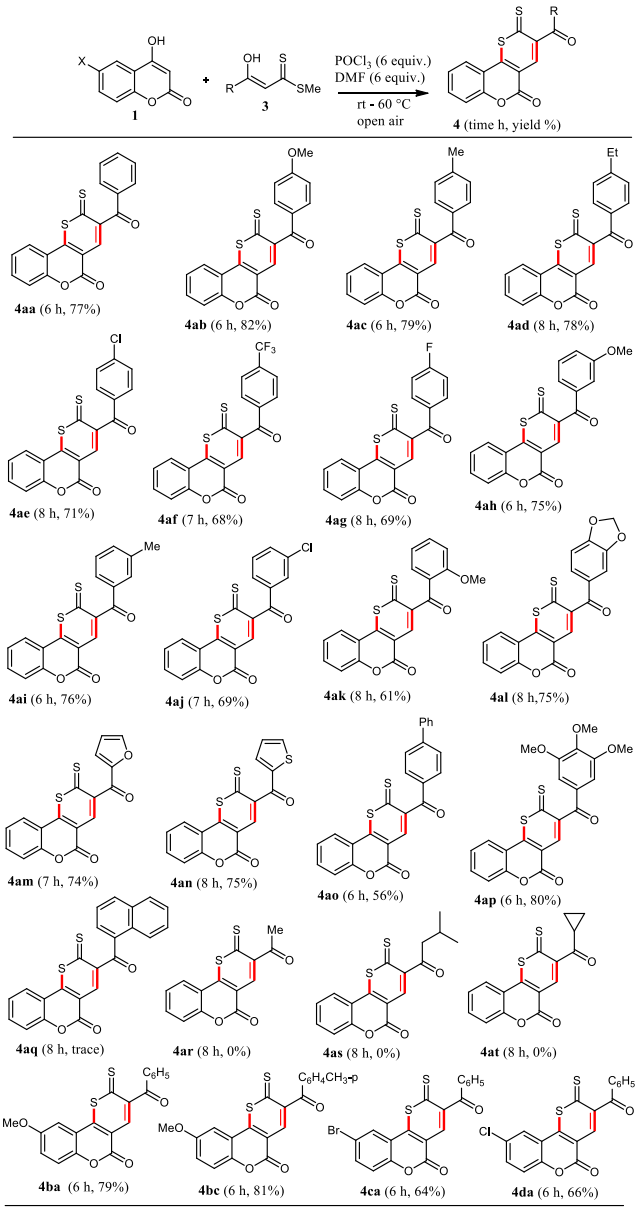
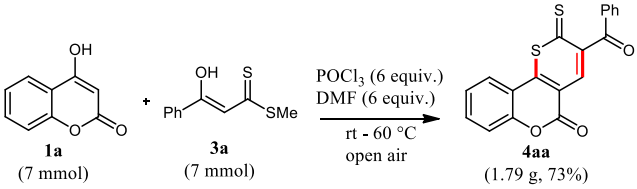
Remarkably, α-enolic dithioesters bearing R moiety as hetaryl groups such as 2-furyl and 2-thienyl were also well suited affording the corresponding products in 74% and 75% yield, respectively (Table 2, **4am** and **4an**). Further in a challenging case, in which R moiety as extended aromatic biphenyl group provided the desired product **4ao** in 56% yield. Noticeably, even more challenging case where three strong electron-donating methoxy groups at R moiety was also found to be compatible for the formation of desired product **4ap** in 80% yield. However, only a trace amount of product was observed on TLC plate in case of R moiety as naphthyl group, which could not be isolated **4aq**.

Table 2. Substrate scope.



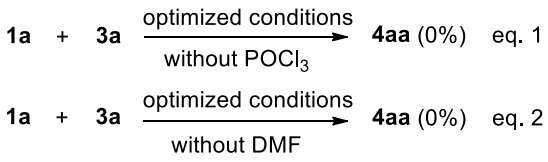
We attempted the synthesis of α-enolic aryldithioesters from substituted acetophenones bearing NO_2, OH and NH_2 groups, but could not get the desired dithioesters. In addition, we also performed the reaction employing dithioesters derived from aliphatic ketones bearing R as methyl, isobutyl and cyclopropyl groups. In all these cases, even a trace of the desired product was not obtained (Table 2, **4ar**, **4as** and **4at**), which limit the scope of the reaction to some extent. This could be due to less stability of aliphatic dithioesters than aromatic dithioesters. Further to check the versatility of the reaction, we surveyed the scope of substituted coumarins. Thus, we employed coumarins bearing electron-donating and electron-withdrawing groups at phenyl ring under the standard condition, the corresponding products (Table 2, **4ba, 4bc, 4ca, 4da**) were obtained in good yields, revealing synthetic utility and broad scope of the reaction.

To illustrate the practical application of this protocol, we performed a gram-scale experiment with **1a** (7 mmol) and **3a** (7 mmol) under the standard reaction conditions (Scheme 2). The desired product 3-benzoyl-2-thioxothiopyrano[3,2-*c*]chromen-5(2*H*)-one (**4aa**) was obtained in 73% yield (1.79 g), which is comparable to the small scale experiment. This result suggests that the present method could be easily adapted for a large-scale preparation.



Scheme 2. Gram-scale synthesis of **4aa**.

To have deep insight into the mechanism for the reaction, we performed some control experiments (Scheme 3). In the absence of $POCl_3$, under standard condition, the desired product **4aa** was not observed even in trace (Scheme 3, eq.1). Similar result was observed in the absence of DMF also (Scheme 3, eq. 2). Thus, use of only $POCl_3$ or DMF alone could not trigger the reaction, which shows that formylating reagent ($POCl_3$-DMF), which generates the reactive species 4-chloro-3-formyl coumarin in situ, is necessary for the reaction. During the course of the reaction, we observed the formation of intermediate 4-chloro-3-formyl coumarin (**2**) on TLC plate.



Scheme 3. Control experiments.

The structural elucidation of all the newly synthesized compounds **4** was determined by their satisfactory spectral (^{1}H and ^{13}C NMR, and HRMS) studies. Furthermore, the structure of one of the representative compounds **4aa** was unequivocally

confirmed by single crystal X-ray diffraction analysis (Figure 1, see Supporting Information for details).[13]

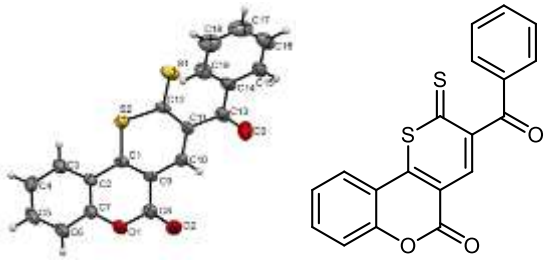
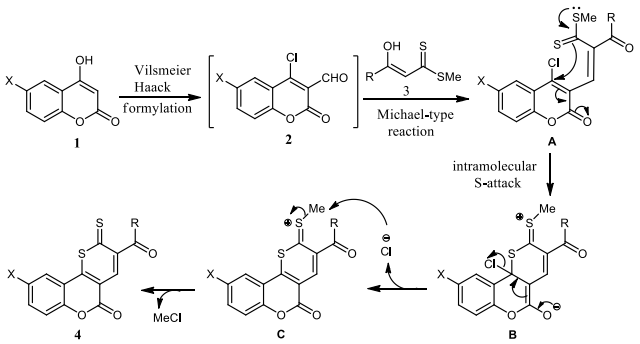


Figure 1. ORTEP diagram of compound **4aa** (CCDC 1923182).

Based on our experimental observations, the following plausible mechanism for the formation of thiopyran annulated coumarins **4** has been suggested (Scheme 4). The first step is supposed to be the Vilsmeier-Haack formylation of 4-hydroxy-coumarin **1** to give 4-chloro-3-formyl coumarin **2**, which has been isolated and fully characterized. Thus, *in situ* generated intermediate **2** undergoes Michael-type addition with α-carbon of dithioester **3** to form intermediate **A**. Intermediate **A** undergoes intramolecular S-cyclization forming C(sp^2)–S bond to give enolate ion intermediate **B**. The eliminated chloride ion from intermediate **B** attacks on intermediate **C**, enabling the cleavage of C(sp^3)–S bond to form the desired annulated coumarin **4** by elimination of methyl chloride. To authenticate the reaction mechanism, we recorded HRMS of reaction mixture. We did not observe any peak of eliminated methyl chloride, which could be due to its gaseous nature. Next, we performed the reaction with α-enolic dithioester bearing *n*-butyl group instead of methyl group of thioalkyl, and recorded the HRMS of reaction mixture. In this case, we found the desired peak of butyl chloride suggesting the elimination of alkyl chlorides during the course of the reaction (see Supporting Information for details).



Scheme 4. Plausible mechanism for the formation of thiopyran annulated coumarins **4**.

In summary, we have developed an efficient domino protocol to access versatile tricyclic 2-thioxothiopyrano[3,2-*c*]chromen-5(2*H*)-ones by the reaction of coumarins with α-enolic dithioesters via consecutive C–C and C(sp^2)–S bonds formation. The reaction involves cross-coupling of α-enolic dithioesters with in situ generated 4-chloro-3-formyl coumarin via Michael-type addition/intramolecular cyclization/elimination cascade sequence. Thus, the construction of thioxothiapyrano annulated coumarin derivatives by this operationally simple protocol expands the coumarin derivatives toolbox, which could be of further biological significance. The clean reaction profile, transition-metal-free conditions, tolerance of wide functional groups, avoidance of expensive/toxic reagents, and CH_3Cl being only by-product are additional attributes to this novel one-pot strategy. This heteroannulation based platform illustrates not only the synthesis of previously inaccessible and synthetically demanding annulated coumarins, but also enriches the chemistry of α-enolic dithioesters. The future portends even greater and richer implementations of this unique synthon to a vast range of other synthetic and material science applications.

Experimental Section

The precursor 4-hydroxy-2*H*-chromen-2-one (**1**) and its derivatives were synthesized by the reaction of 1-(2-hydroxyphenyl)ethanone with dialkyl carbonate in the presence of sodium hydride in accordance with the literature reports.[14] The in situ generation of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **2** has been done by treating 4-hydroxy-2*H*-chromen-2-one with $POCl_3$/DMF mixture as formylating reagents under Vilsmeier conditions.[15] α-Enolic dithioesters **3** are not commercially sourced, and were synthesized in good yields following the reported procedure.[16] To an ice-cooled stirred solution of 4-hydroxy-2*H*-chromen-2-one (**1**) (0.25 mmol, 1 equiv.) in DMF (6 equiv.), $POCl_3$ (6 equiv.) was added drop wise over a period of 5 min. The reaction mixture was allowed to stir at room temperature for 30 min. The temperature of the reaction was increased to 60 ^{0}C followed by the addition of α-enolic dithioester **3**. The reaction mixture was further stirred till the completion of the reaction. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with 30 mL of ethyl acetate, followed by washing with saturated $NaHCO_3$ solution (2 × 50 mL) to neutralize the acid formed during the course of the reaction. The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography over silica gel (100−200 mesh) using hexane-ethyl acetate (9:1) as eluent to give the pure products **4**.

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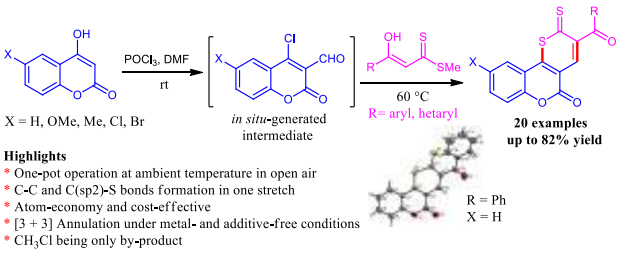
COMMUNICATION

Metal- and Catalyst-Free One-Pot Cascade Coupling of α-Enolic Dithioesters with in situ Generated 4-Chloro-3-formylcoumarin: Access to Thioxothiopyrano[3,2-*c*]chromen-5(2*H*)-ones



Highlights

* One-pot operation at ambient temperature in open air
* C-C and C(sp2)-S bonds formation in one stretch
* Atom-economy and cost-effective
* [3 + 3] Annulation under metal- and additive-free conditions
* CH_3Cl being only by-product

R = Ph
X = H

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