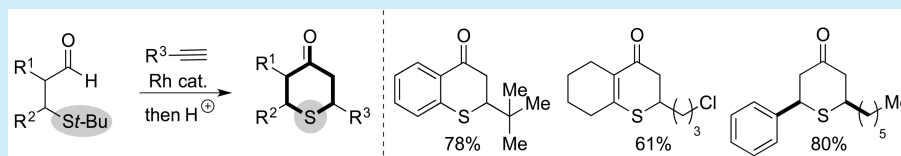


Two-Component Assembly of Thiochroman-4-ones and Tetrahydrothiopyran-4-ones Using a Rhodium-Catalyzed Alkyne Hydroacylation/Thio-Conjugate-Addition Sequence

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S Supporting Information



ABSTRACT: β' -Thio-substituted-enones, assembled from the combination of β -*tert*-butylthio-substituted aldehydes and alkynes, using rhodium catalysis, are shown to smoothly undergo in situ intramolecular S-conjugate addition to deliver a range of S-heterocycles in a one-pot process. Aryl, alkenyl, and alkyl aldehydes can all be employed, to provide thiochroman-4-ones, hexahydro-4*H*-thiochromen-4-ones, and tetrahydrothiopyran-4-ones, respectively. A variety of in situ oxidations are also performed, allowing access to S,S-dioxide derivatives, as well as unsaturated variants.

Recent years have seen the emergence of alkene and alkyne hydroacylation reactions as useful methods for the synthesis of ketones and enones, respectively.¹ For metal-catalyzed variants,^{2–5} strategies based on the use of some form of chelation control, with the coordinating group pendant to the aldehyde^{6–10} or alkene/alkyne,¹¹ have been shown to deliver efficient, selective reactions,^{6c,7b,12,11b,13} with a generally broad substrate scope. The inherent limitation of a chelation-controlled approach is that the coordinating substituent, which is crucial to achieve a successful reaction, is inevitably present in the product. Approaches to mitigate this situation include exploiting the coordinating group in subsequent catalyst-controlled transformations,¹⁴ and also incorporating the group, usually via derivatization, into a target structure. In the context of this latter strategy, our laboratory demonstrated that dihydroquinolones could be conveniently prepared from an alkyne hydroacylation/*N*-conjugate addition sequence commencing with 2-aminobenzaldehyde substrates.^{7c} More recently, the Stanley group reported the development of a tandem alkyne hydroacylation/oxa-Michael addition process to synthesize *trans*-2,3-disubstituted chroman-4-ones from *O*-chelating benzaldehydes (Scheme 1a).¹⁵ In this Letter we show that S-chelating aldehydes can be used to access a variety of S-heterocycles from related hydroacylation/conjugate addition sequences (Scheme 1b). A crucial difference with the present study is that the use of S-chelating aldehydes allows access to heterocycles of much greater variety than either the *N*- or *O*-based chemistries.

Thiochromanones and related heterocycles, notably S,S-dioxide derivatives and unsaturated variants, are present in a number of medically relevant molecules (Scheme 1c),¹⁶ and as such we envisaged a general synthetic route that would allow access to a broad range of related S-heterocycles. Our approach

is shown in Scheme 1b and involves chelate-controlled alkyne hydroacylation followed by an acid triggered thio-conjugate addition.¹⁷ Although encouraging precedent is provided from our own reports of hydroquinolone synthesis,^{7c} and Stanley's chroman-4-one chemistry,¹⁵ both of these sequences are limited to aryl aldehyde substrates, thus constraining the structural variation accessible in the products. Of the chelating aldehydes that have been reported, S-substituted examples allow arguably the most structural variation with alkyl,^{8a} alkenyl,^{12c} aryl,^{8c} and heteroaryl¹⁸ derivatives all being competent substrates. We reasoned that exploiting this feature of S-chelation control would allow access to not only thiochromanones but also the related saturated and partially saturated derivatives.

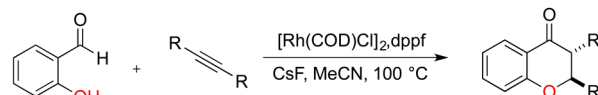
Our general approach requires aldehyde substrates bearing a sulfide substituent that would ideally be cleaved under the cyclization conditions. Given the proposed acid mediated cyclization (i.e., I \rightarrow II \rightarrow III, Scheme 1b) we settled on the use of *t*-Bu-sulfides.¹⁹ Although β -*t*-Bu-S-substituted aldehydes have never been previously reported as substrates for alkene or alkyne hydroacylation, we were pleased to find that the use of established reaction conditions, developed mainly for β -Me-S-substituted variants, led to efficient hydroacylation.²⁰ For example, coupling between 2-*tert*-butyl-sulfide-substituted benzaldehyde 1a and 4-tolylacetylene using 5 mol % of commercially available Rh(nbd)₂BF₄ and the dcpm ligand in 1,2-dichloroethane at 55 °C resulted in quantitative formation of the enone product. A short investigation of possible cyclization conditions established that in situ treatment of the

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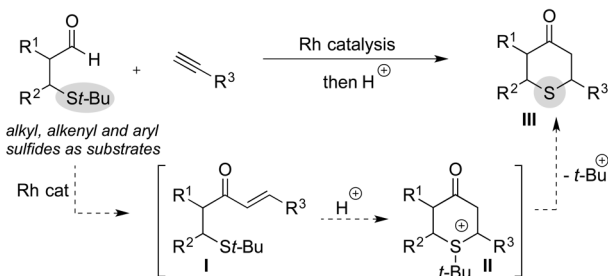
Scheme 1. Tandem Hydroacylation/Conjugate Addition Sequences Towards Heterocycles, Together with Biologically Relevant S-Heterocycles

a) Tandem alkyne hydroacylation/oxa-Michael addition (Stanley, 2015)

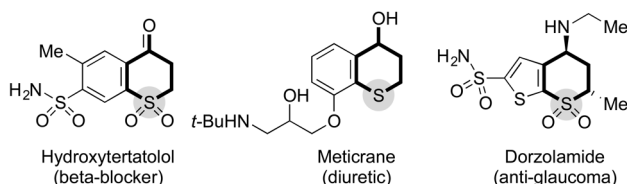


limited to phenolic aldehydes as substrates

b) Tandem alkyne hydroacylation/thio-conjugate addition (*this work*)



c) Examples of biologically active thiochroman-4-ones and derivatives

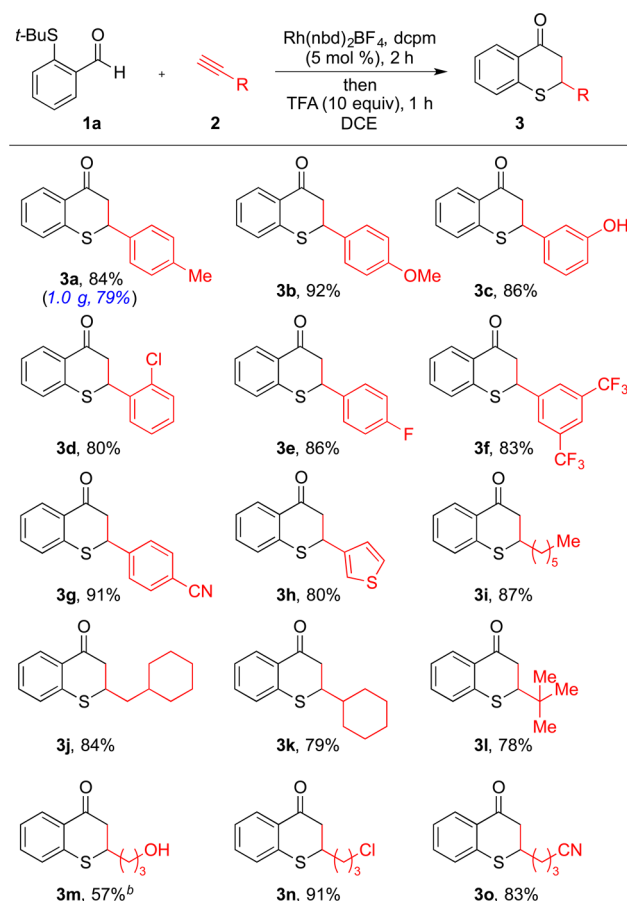


hydroacylation adduct with excess trifluoroacetic acid (TFA) resulted in clean conversion to the S-heterocycle.

Scheme 2 shows our exploration of these reaction conditions using aldehyde **1a** in combination with a range of alkyne substrates (**2**). The transformation was successfully applied to phenyl acetylene derivatives bearing a variety of electron-donating (**3a–c**) and electron-withdrawing groups (**3d–g**). Substituents on the alkyne moiety were tolerated at all positions of the benzene rings. Notable among those examples is **3c**, which has been reported as a potent antioxidant displaying high inhibitory activity against nitric oxide production.^{16f} The tandem reaction was also achieved employing reactive cyano groups (**3g**, **3o**) and a simple heterocycle (**3h**). Alkynes possessing aliphatic chains also afforded thiochroman-4-ones in excellent yields (**3i–o**), even when employing a bulky *tert*-butyl substituent (**3l**). Pleasingly, the tandem process was also found to be applicable on a gram scale reaction using 4-tolylacetylene, with only 1 mol % of rhodium catalyst and ligand delivering the final product in comparable yield.

We next examined the scope of the aldehyde component (**Scheme 3**). A variety of 2-(*tert*-butylthio)benzaldehyde derivatives (**1**) were combined with 4-tolylacetylene, delivering diversely substituted thiochroman-4-ones possessing electron-donating (**3p**, **3q**, **3u**) and electron-withdrawing (**3r–u**) functional groups in moderate to excellent yields. The use of an alkenyl derived S-chelating aldehyde led to thiochromen-4-one **3v** in good yield. Pleasingly, tetrahydrothiopyran-4-ones could also be accessed (**3w–y**) with acceptable yields and diastereoselectivities. The tandem process was also found to be applicable to internal alkynes, enabling the formation of tetrahydrothiopyran-4-one **3z** featuring three stereogenic centers. Employing the same internal alkyne in combination with aromatic aldehyde **1a** was also a successful reaction;

Scheme 2. Variation of Alkyne Structure in the Formation of Thio-4-chromanones^a



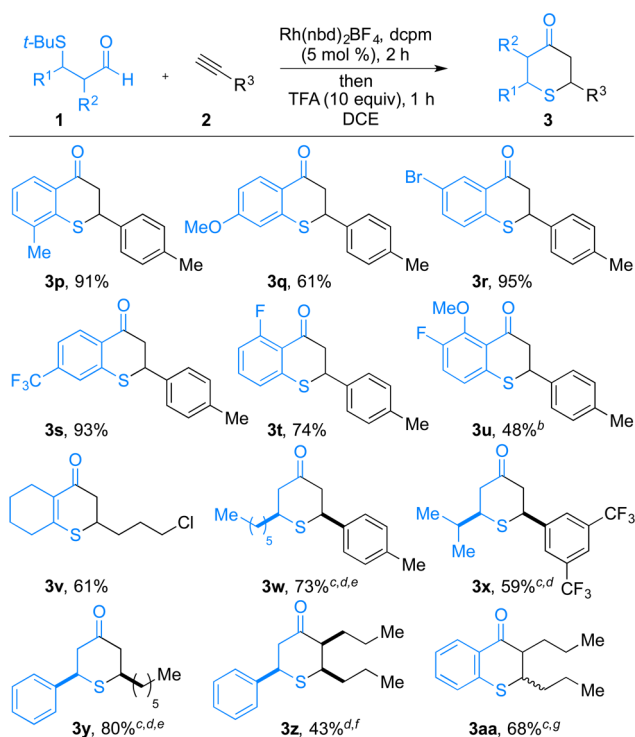
^aReaction conditions: Rh(nbd)₂BF₄ (5 mol %), dcpm (5 mol %), aldehyde **1a** (1.0 equiv), alkyne (1.05 equiv), DCE (1.0 M), 55 °C, 2 h, then TFA (10.0 equiv), 1 h, rt. ^bK₂CO₃, MeOH, 16 h, rt, after acid step. Isolated yields.

however, in this case the disubstituted thiochroman-4-one (**3aa**) was obtained as an inseparable 1:1.8 mixture of diastereomers. This level of diastereoselectivity is consistent with that seen by Stanley for the corresponding chroman-4-one series.¹⁵

Aware that the S,S-dioxide derivatives of thiochromanones and tetrahydrothiopyranones are of interest as medicinal agents, we adapted our process to allow access to this class of compounds directly (**Scheme 4**). Simply adding an aqueous solution of hydrogen peroxide at the completion of the cyclization step resulted in oxidation to the desired sulfone derivatives. Aryl- and alkyl-substituted thiochromanones (**4a,b**), together with an alkyl-substituted tetrahydrothiopyranone (**4c**), provided the oxidized products in moderate to good yields.

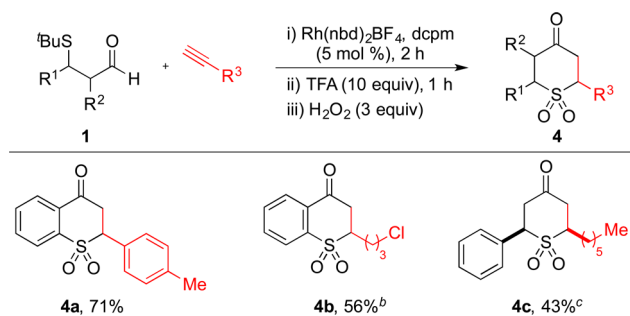
We developed a further modification of our hydroacylation-based route to S-heterocycles, whereby addition of N-chlorosuccinimide (NCS) subsequent to S-conjugate addition allowed access to thiochromenone and dihydrothiopyran-4-one derivatives (**Scheme 5**). Following a report from Chen,²¹ we investigated the addition of NCS directly to the reaction mixtures. However, the excess TFA used to promote the S-cyclization was incompatible with this approach. The solution was to remove the excess TFA *in vacuo* before addition of the NCS and pyridine to the crude reaction mixture. Using this

Scheme 3. Variation of Aldehyde Structure in the Formation of Thiochroman-4-ones, Thiochromen-4-ones, and Tetrahydrothiopyran-4-ones^a



^aIsolated yields of pure diastereomers. Reaction conditions: Rh(nbd)₂BF₄ (5 mol %), dcpm (5 mol %), aldehyde (1.0 equiv), alkyne (1.05 equiv), DCE (1.0 M), 55 °C, 2 h, then TFA (10.0 equiv), 1 h, rt. ^bRh(nbd)₂BF₄ and dcpm (both 7.5 mol %). ^calkyne (1.2 equiv). ^dCrude dr values: 3w: 15:1, 3x: 19:1, 3y: 17:1, 3z: 11.5:2.1:1.5:1.0. ^eProduct contains traces of the minor diastereomer. ^fRh(nbd)₂BF₄ and dppm (both 10.0 mol %), alkyne (1.5 equiv), DCE (1.0 M), 80 °C, 2 h. ^gdppm (5 mol %) used in place of dcpm. Isolated as an inseparable 1:1.8 mixture of diastereomers.

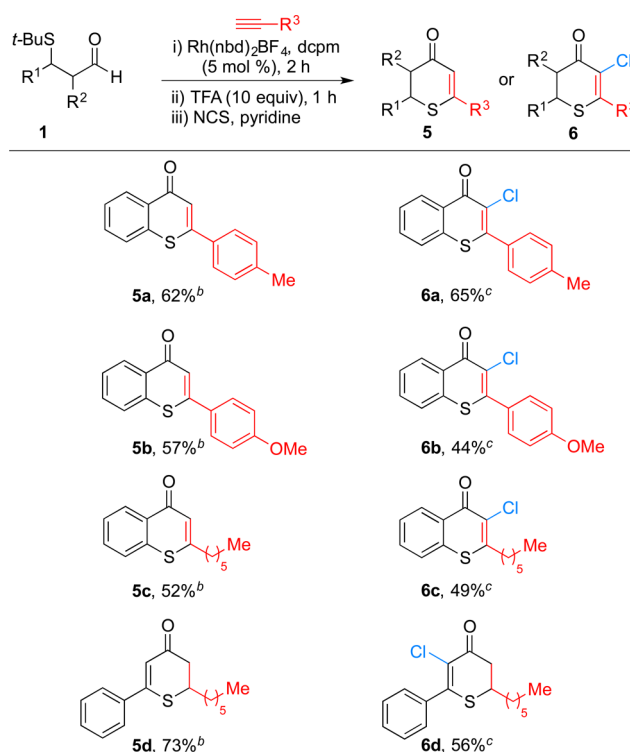
Scheme 4. In Situ Preparation of S,S-Dioxide Derivatives^a



^aReaction conditions: (i) Rh(nbd)₂BF₄ (5 mol %), dcpm (5 mol %), aldehyde 1a (1.0 equiv), alkyne (1.05 equiv), DCE (1.0 M), 55 °C, 2 h; (ii) TFA (10.0 equiv), 1 h, rt; (iii) H₂O₂ (3.0 equiv), rt. Isolated yields. ^bH₂O₂ (4.5 equiv). ^cCrude dr 19:1.

approach we were able to access both thiochromen-4-ones and dihydrothiopyran-4-ones in good yields after three steps (5a–d). As suggested by Chen, addition of excess NCS and pyridine provided the α -chloro adducts (6a–d). It is interesting to note the selective formation of dihydrothiopyranones 5d and 6d where oxidation has taken place adjacent to the aryl substituent.

Scheme 5. NCS-Mediated Formation of Thiochromenones and Dihydrothiopyranones^a



^aReaction conditions: (i) Rh(nbd)₂BF₄ (5 mol %), dcpm (5 mol %), aldehyde (1.0 equiv), alkyne (1.05 equiv), DCE (1.0 M), 55 °C, 2 h; (ii) TFA (10.0 equiv), 1 h, rt. ^bNCS (1.1 equiv), pyridine (1.1 equiv), DCE (0.5 M), rt, 2 h. ^cNCS (3.0 equiv), pyridine (3.0 equiv), DCE (0.5 M), rt, 2 h. Isolated yields.

In conclusion, we have developed a tandem alkyne hydroacylation/thio-conjugate addition sequence to synthesize thiochroman-4-one, hexahydro-4H-thiochromen-4-one, and tetrahydrothiopyran-4-one derivatives, and their corresponding sulfones, from readily accessible starting materials. The addition of NCS and pyridine as a final step in the sequence allowed for the preparation of thiochromen-4-ones and dihydrothiopyran-4-ones, as well as their chlorinated derivatives. The key hydroacylation step exploits β -(*t*-Bu-S)-substituted aldehydes as substrates for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02909.

Experimental procedures and full characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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