Synthetic Methods

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Efficient Synthesis of Thiopyrans Using a Sulfur-Enabled Anionic Cascade**

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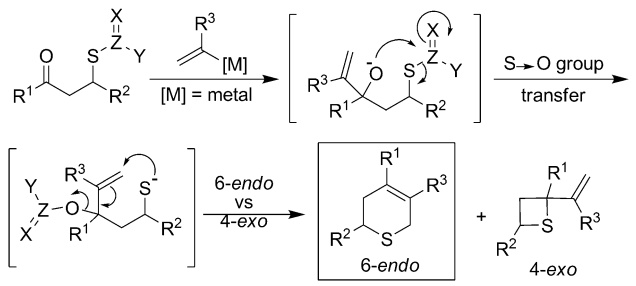
Sulfur is the fifth most important element, following carbon, hydrogen, oxygen, and nitrogen, in the context of biological significance and representation in important natural and nonnatural constructs. Its unique properties also make it one of the most chemically versatile of the early elements. For example, sulfur compounds are: 1) great nucleophiles; 2) readily reduced and oxidized; 3) good at stabilizing carbanions and carbocations; 4) a source of useful ylide and umpolung chemistry; 5) of great utility in radical chemistry; 6) able to be chiral at sulfur; 7) found in the cores of important chiral auxiliaries, and 8) the key enabling element for more than twenty name reactions in organic chemistry.[1] In terms of pharmaceuticals, sulfur is solidly the most significant and successful element following the four key elements of life (C, H, N, and O), with seven of the ten best-selling pharmaceuticals worldwide containing sulfur.[2]

As a part of our program focused on the development of new useful synthetic transformations involving sulfur as the central element,[3] we report a new anionic cascade[4] that provides convergent access to thiopyran products[5] in a single pot from simple starting materials (Scheme 1). The inspiration for the design of this new reaction originated from a desire to extend our ring expansion investigations to include vinyl thietanes, which we envisioned could be converted into a thiopyran upon treatment with a metal catalyst. Intrigued by the simple and convergent thiirane synthetic approach we had utilized for our formal synthesis of biotin, we postulated that the thiopyran constructs could possibly be accessed in a single step from an appropriately functionalized carbonyl construct containing a thiol group at the β position instead of a ring expansion path. This new one-pot anionic cascade would be initiated upon addition of a vinyl nucleophile to the carbonyl group, at which point the substitutent on sulfur migrates to the newly formed alkoxide, thus forming a new leaving group and a thiolate nucleophile. Ketones and esters were expected to be the most suitable substrates for this new anionic cascade. Tertiary substitution of the alkoxide, formed by coupling the two carbon fragments together, was expected to ensure preference for the desired 6-*endo* cyclization pathway over the competing 4-*exo* pathway.



Scheme 1. One-pot anionic cascade route to thiopyrans.

The most critical part of the reaction design was the nature of the thiol substitutent (XYZ; Scheme 1). A suitable substitutent would be required to 1) survive the addition of the carbon nucleophile, 2) readily transfer from sulfur to the alkoxide, and 3) transform the alkoxide into a good leaving group. Literature precedents suggested three structural frameworks that might fit our criteria: 1) thiocarbonate- or xanthate-type acyl groups,[6] 2) thio-substituted heterocycles,[7] or 3) phosphates.[8] Phosphates were chosen as the group to study the feasibility of the anionic cascade because of their ease of substrate synthesis, stability toward carbon nucleophiles, and leaving group ability (Z = P, Y = OR and X = O or S; Scheme 1).

To test our hypothesis, we chose to explore the addition of vinyl nucleophiles to the aryl ketone thiophosphate **1** (Table 1). The addition product would afford a tertiary alkoxide, which would then undergo a migration of the thiophosphate to form a thiolate nucleophile, which we expected would favor the 6-*endo* cyclization pathway. Vinyl Grignard addition to the aryl ketone **1** proceeded well to form **2** without interference from the thiophosphate group. Interestingly, in tetrahydrofuran with magnesium as the alkoxide counterion, the expected in situ anionic cascade to form **3** or **4** did not take place. Instead, the corresponding alcohol was isolated (entry 1).

Presumably the magnesium counterion impedes thiophosphate transfer to the alkoxide. However, treatment of the corresponding alcohol with an alkoxide base or sodium hydride resulted in a facile cyclization, which afforded the thiopyran **3** as the major product following an acidic workup.[9] We postulated that an alkali metal alkoxide additive might exchange out the magnesium in situ and allow the proposed anionic cascade to proceed in one pot (Table 1, entries 2–13). After screening lithium, sodium, and potassium alkoxides in methanol, ethanol, 2-propanol, or *tert*-butanol, it became clear that adding potassium *tert*-butoxide

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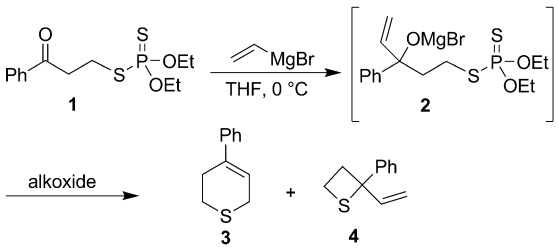
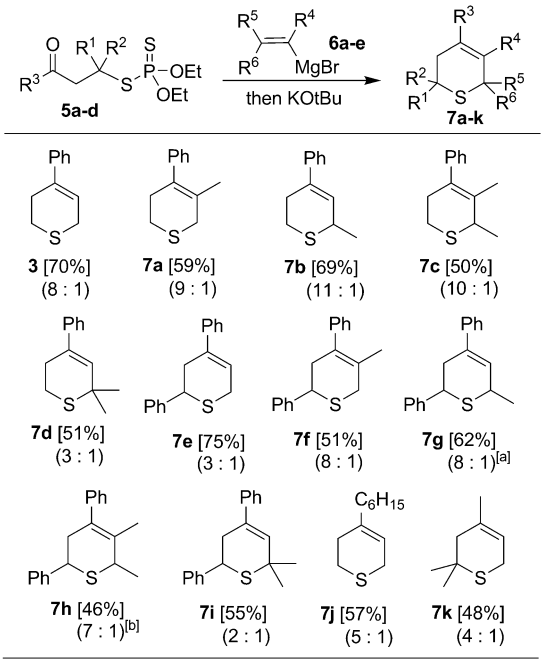
Table 1: Optimization studies for one-pot anionic cascade.



Entry	Alkoxide[a]	*t*	**3**/**4**[b]	Yield [%][c]
1	none	1 h	–	0[d]
2	**KO*t*Bu**	**5 min**	**7.5:1**	**70**
3	KO*i*Pr	5 min	8:1	58
4	KOEt	12 h	7:1	48
5	KOMe	20 h	6.5:1	51
6	NaO*t*Bu	20 h	7:1	55
7	NaO*i*Pr	24 h	7:1	41
8	NaOEt	48 h	6:1	47
9	NaOMe	72 h	6:1	42
10	LiO*t*Bu	72 h	–	trace[d]
11	LiO*i*Pr	72 h	–	trace[d]
12	LiOEt	1 week	–	0[d]
13	LiOMe	1 week	–	0[d]

[a] 3 equivalents. [b] Thiopyran/thietane product ratio after HCl workup. [c] Yield of isolated product. [d] Protonated form of **2** (alcohol) isolated in 75% yield.



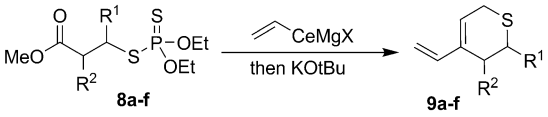
Scheme 2. One-pot synthesis of thiopyrans. Given yield is that of the isolated product and the thiopyran/thietane product ratio is given within parentheses. [a] 1.5:1 *trans*/*cis*-2,6-thiopyran ratio; [b] 1.2:1 *trans*/*cis*-2,6-thiopyran ratio.

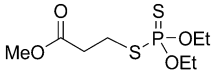
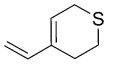
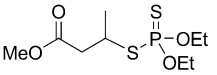
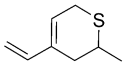
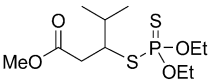
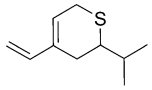
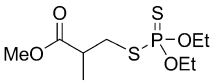
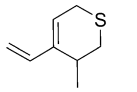
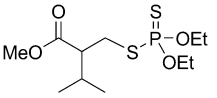
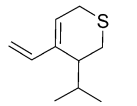
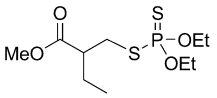
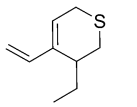
(entry 2) to the crude mixture resulted in the cascade proceeding rapidly to completion. The smaller the alcohol, and the tighter the binding to the counterion the slower the counterion exchange.

This new one-pot cascade reaction could indeed be generalized. Twelve successful examples are presented in Scheme 2. These products (**7a**–**k**) were accessed in high yields and in one pot by first subjecting the keto thiophosphates **5a**–**5d** to four different vinyl Grignard reagents (**6a**–**d**) and then adding 1.1 equivalents of potassium *tert*-butoxide to the intermediate magnesium alkoxide. In all cases the intermediate thiolate cyclized to form the desired product. The thiopyran products **7g** and **7h** were obtained as mixtures of isomers, which modestly favored the 2,6-*trans* diastereomer. It is worth noting that, although THF was a well suited solvent to ensure both a high yielding Grignard addition and efficient in situ cyclization, it was not always the best solvent for achieving the highest 6-*endo*/4-*exo* cyclization ratios. For example, when the protonated form of **2** was independently treated with a base in different solvents, acetonitrile and dimethylsulfoxide emerged as being superior to tetrahydrofuran with respect to cyclization ratios (overall yields are equivalent for the substrates shown). Thus, depending on the thiopyran substrate being pursued, treating the crude vinyl carbinol with a base in acetonitrile might on occasion provide better results than when employing the one-pot approach.

This success prompted us to evaluate the potential of the esters **8** (Table 2) as suitable cascade substrates.[10] The resulting 1,3-diene products would be of greater synthetic interest. Conversion of the esters into the desired divinyl alkoxides failed with Grignard and lithium reagents, but was accomplished using the less basic vinyl cerium counterparts.[11] The resulting cerium alkoxides where more challenging to exchange in situ than the magnesium alkoxides. The thiopyran products (**9a**–**f**) were obtained in high yields by

Table 2: Synthesis of 4-vinyl thiopyrans.

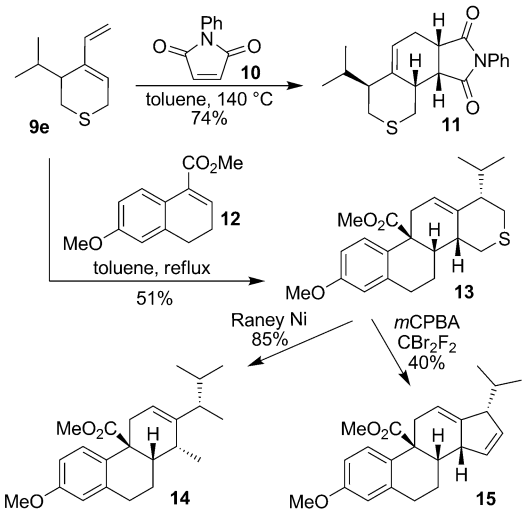


Entry	Substrate	Product	Yield [%][a]
1			70 (85)
2			71 (79)
3			69 (81)
4			73 (78)
5			71 (83)
6			68 (85)

[a] Yield of the isolated thiopyran. Yield within parentheses is that of the crude divinyl carbinol.

treating the crude divinyl carbinol intermediates with potassium *tert*-butoxide.

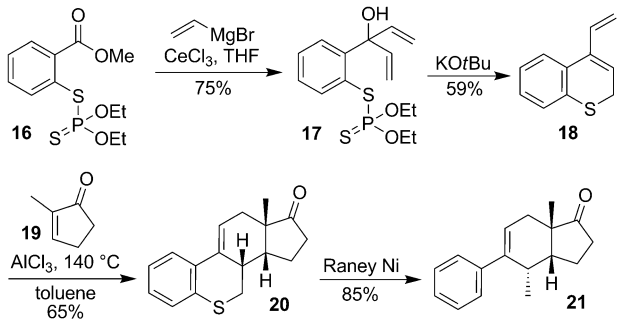
As a demonstration of the usefulness of these products, we reacted diene **9e** with *N*-phenylmaleimide (**10**, Scheme 3) and were delighted to find that a single diasteromer (**11**) was



Scheme 3. Expedient synthesis of steroidal scaffolds. *m*CPBA = *meta*-chloroperbenzoic acid.

produced. Furthermore, upon treatment with styrene **12**,[12] the thiosteroidal construct **13**[13] was obtained in high yield using only a two-pot reaction sequence. To further demonstrate the power and versatility of sulfur in synthesis, **13** was separately reduced[14] (**14**) and ring contracted[15] (**15**) to afford complex products that do not contain sulfur but owe their efficient assembly to sulfur.

We wondered if this new anionic cascade could be extended to include phosphate-capped thiophenol substrates. Towards that end, the thioester **16** (Scheme 4) was obtained in one step from commercially available methyl 2-mercapto-



Scheme 4. Expedient synthesis of a rare thiosteroid core.

benzoate. Indeed, the anionic cascade could be realized using the conditions developed for alkyl ester substrates, thereby affording the diene **18** in good yield. To demonstrate the synthetic potential of this product we performed a Diels–Alder reaction between **18** and the enone **19**, thus affording the thiosteroid scaffold **20**.[16] When the sulfur atom was reductively removed, a complex indene product (**21**) resulted.

This new method for synthesizing 3,6-dihydro-2H-thiopyran scaffolds is broader in scope and more versatile than currently existing methods, which rely on unstable thiocarbonyl groups,[17] vinylphosphonium precursors,[18] expensive catalysts,[19] or complex starting materials.[20] Most commonly, 3,6-dihydro-2H-thiopyran products are accessed from intermediates like 4-oxothianes by addition and subsequent dehydration or enolatization and cross couplings. These approaches not only use additional steps but commonly suffer from the lack of control in forming the thiopyran double bond, the same limitation that the thiocarbonyl cycloaddition strategy is plagued by when unsymmetrical dienes are used.

In summary, we report a new method for synthesizing thiopyran products from readily available building blocks. This programmed anionic cascade is dependent upon substrate structure, sulfur substituents, and reaction conditions to proceed in a single pot. The method works for β-substituted ketones and esters using either alkyl or aryl thiolate partners. Furthermore, we have demonstrated that the concept can be extended to thiophenols. The nineteen examples presented herein serve as a testament to the usefulness and versatility of this new method. The 1,3-diene containing thiopyran products provide access to highly complex scaffolds when coupled with a Diels–Alder reaction and sulfur specific transformations. By coupling this new strategy to asymmetric conjugate addition of thionucleophiles to enones and enoates, access could be provided to chiral building blocks. Future efforts are focused on utilizing this one-pot anionic cascade blueprint to access alternate useful heterocyclic frameworks.

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to thiopyrans. This is the first known example of such a ring expansion reaction.
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