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Pyridinedithioesters as Heterodienophiles: Application to the Synthesis of Aprikalim§

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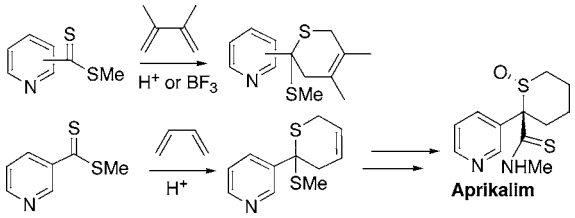
ABSTRACT



Pyridinedithioesters can be used as efficient heterodienophiles when activated by complexation with BF_3, by protonation, or by oxidation of the nitrogen atom of the pyridine moiety. The hetero-Diels–Alder reaction using 3-pyridinedithioester as a heterodienophile was the key step in a new synthesis of Aprikalim in racemic form. The methodology can be reliably extended to prepare new analogues of Aprikalim.

Aprikalim belongs to a class of bioactive molecules called potassium channel activators.[1] In the main approach to synthesize Aprikalim, the step leading to the thiapyran *S*-oxide moiety is an intramolecular alkylation involving the 3-picolyl-4-chlorobutyl sulfoxide as substrate.[1c] For the synthesis of an Aprikalim analogue, in which the 3-(trifluoromethyl)benzene replaced the pyridine moiety, a hetero-Diels−Alder (HDA) reaction using a thioketoester as a heterodienophile to generate the thiapyran heterocycle was reported.[2] To our knowledge, the HDA reaction with a thiocarbonyl compound as a heterodienophile has never been used to prepare Aprikalim. Because dithioesters are efficient heterodienophiles when substituted in the α-position by an electron-withdrawing group[3] (CN,[4] CO_2R,[5] CF_3,[6] SO_2R,[7] $(RO)_2P(O)$,[8] $(RO)_2P(O)CF_2$[9]), which lowers the LUMO energy of the heterodienophile, we believed that 3-pyridinedithioester **1a**, which is the sulfur analogue of the nicotinic ester, can be a versatile precursor for the synthesis of bioactive molecules such as Aprikalim or various other nicotinic derivatives. To activate the dienophilicity of pyridinedithioesters **1**, a Lewis acid or a Brönsted acid directly

§ Dedicated to Dr. Serge Masson.

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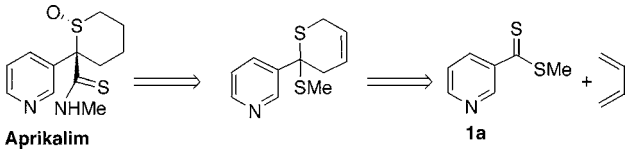
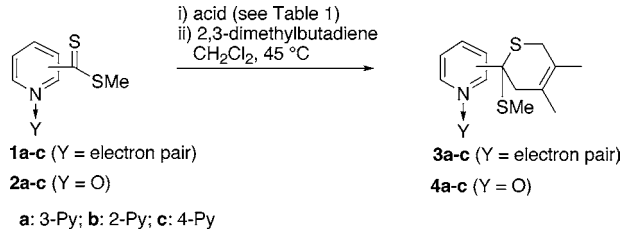
bonded to the pyridine nitrogen atom should lower the π-electron density of the aromatic ring. Consequently, the pyridine heterocycle will be more electron withdrawing, affording a more reactive thiocarbonyl heterodienophile. For the same reason, an *N*-oxide pyridine moiety can also activate the thiocarbonyl group. We report here the first study of the reactivity of pyridinedithioesters as heterodienophiles and, as a preliminary synthetic application, a new synthesis of racemic Aprikalim using 3-pyridinedithioester **1a** as a heterodienophile. The retrosynthetic analysis is presented in Scheme 1.

Scheme 1. Retrosynthetic Analysis of Aprikalim from 3-Pyridinedithioester **1a**



First, we examined the reactivity of pyridinedithioesters **1a**−**c** (**1a**, **1b**, and **1c** are, respectively, 3-, 2-, and 4-pyridinedithioesters) and their *N*-oxide counterparts **2a**−**c** toward 2,3-dimethylbutadiene. All dithioesters were prepared by the procedure we already reported.[10] The reactions were carried out in a pressure tube, in dichloromethane, at 45 °C (Scheme 2). As expected, nonactivated dithioester **1a** reacted

Scheme 2. Cycloaddition of Dithioesters **1a**−**c** and **2a**−**c** with 2,3-Dimethylbutadiene



slowly; the conversion into **3a** amounted to 77% after 15 days (Table 1, entry 1). When 1 equiv of BF_3, HCl, or trifluoroacetic acid (TFA) was added to **1a**, the reaction leading to **3a** went faster and was completed in 2−4 days (Table 1, entries 2, 5, and 6). The reaction was also accelerated using a catalytic amount (0.5 or 0.1 equiv) of BF_3, even if the conversion was still incomplete after 2 days (Table 1, entries 3 and 4). *N*-Oxide dithioester **2a** also reacted faster than **1a** allowing a complete conversion of **2a** into **4a** within 7 days (Table 1, entry 10).

Pyridinedithioesters **1b** and **1c** were expected to be more reactive than 3-pyridinedithioester **1a**. With **1b**, the reaction was completed after 7 days, leading to cyclodduct **3b** (Table

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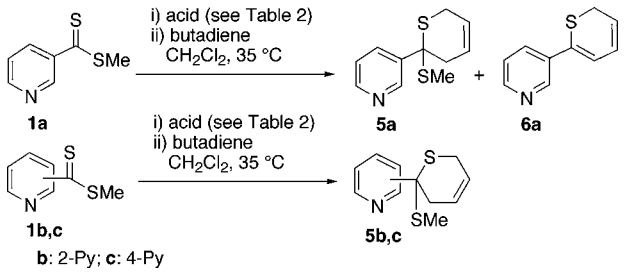
Table 1. Cycloaddition of Dithioesters **1a**−**c** and **2a**−**c** with 2,3-Dimethylbutadiene: Activation of the Dienophile

entry	dithioester	acid (equiv)	product	time	conv %
1	**1a**		**3a**	15 days	77
2	**1a**	BF_3 (1.0)	**3a**	2 days	>98
3	**1a**	BF_3 (0.5)	**3a**	2 days	85
4	**1a**	BF_3 (0.1)	**3a**	2 days	60
5	**1a**	HCl (1.0)	**3a**	4 days	>98
6	**1a**	TFA (1.0)	**3a**	4 days	>98
7	**1b**		**3b**	7 days	>98
8	**1b**	BF_3 (1.0)	**3b**	15 min	>98
9	**1c**	BF_3 (1.0)	**3c**	15 min	>98
10	**2a**		**4a**	7 days	>98
11	**2b**		**4b**	1 h	>98
12	**2c**		**4c**	1 h	>98

1, entry 7). Addition of BF_3 to **1b** allowed a complete conversion in 15 min, leading to **3b** (Table 1, entry 8). A similar result was obtained with **1c** leading to **3c** (Table 1, entry 9). In the *N*-oxide series, dithioesters **2b** and **2c** required only 1 h to be fully converted into cycloadducts **4b** and **4c**, respectively (Table 1, entries 11 and 12).

In a second series of experiments, we examined the reaction of dithioesters **1** with butadiene, which is the appropriate diene to prepare Aprikalim from **1a** (Scheme 3).

Scheme 3. Cycloaddition of **1a**−**c** with Butadiene



Activated by BF_3 (1 equiv), **1a** gave within 24 h the expected cycloadduct **5a** together with a byproduct **6a** (ratio 3:1) in 91% overall yield (Table 2, entry 1). The byproduct was

Table 2. Cycloaddition of Dithioesters **1a**−**c** with Butadiene

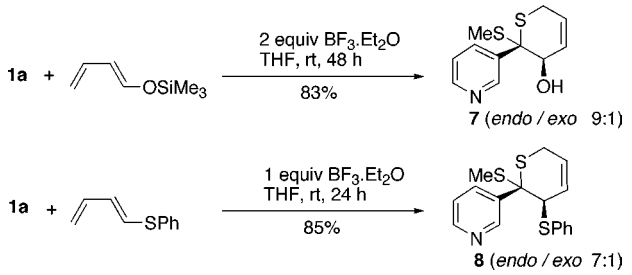
entry	dithioester	acid (equiv)	product (ratio)	time	yield %
1	**1a**	BF_3 (1.0)	**5a/6a** (3:1)	24 h	91
2	**1a**	BF_3 (2.0)	**5a/6a** (1:10)	24 h	47
3	**1a**	HCl (1.0)	**5a**	72 h	78
4	**1b**	BF_3 (1.0)	**5b**	1 h	97
5	**1c**	BF_3 (1.0)	**5c**	1 h	82

identified by NMR as the dehydrosulfanylated adduct **6a**, and its formation was explained by the complexation of BF_3 on the exocyclic sulfur atom of **5a** provoking the elimination of the methylsulfanyl moiety. Moreover, in another experi-

ment using 2 equiv of BF_3, **6a** was obtained as the main product (the **5a**/**6a** ratio was 1:10; Table 2, entry 2). However, the overall yield was low (47%) because of the degradation of **6a** during purification. The N-protonated dithioester **1a** gave only the expected Aprikalim precursor **5a** in 78% yield (Table 2, entry 3). Cycloadditions of butadiene with dithioesters **1b** and **1c**, activated with BF_3, led within 1 h to the corresponding cycloadducts **5b** and **5c**, in good yields (82−97%). In these cases, the formation of the desulfanylated derivatives analogous to **6a** was not observed (Table 2, entries 4 and 5).

To check the accessibility to Aprikalim analogues having a modified thiapyran cycle, we examined the cycloaddition of 3-pyridinedithioester **1a** with functionalized dienes. Two dienes were chosen: 1-trimethylsilyloxybutadiene, which is commercially available, and 1-phenylsulfanylbutadiene, which was synthesized according to literature procedure.[11] In both reactions, dienophile **1a** was activated by BF_3 (Scheme 4).

Scheme 4. Cycloaddition of **1a** with Functionalized Dienes[a]



[a] Only the major endo cycloadducts are given.

In both cases, complete regioselectivity was observed in the cycloaddition. The reaction with 1-trimethylsilyloxybutadiene led to the expected adduct **7**, as a mixture of endo and exo isomers (ratio 9:1) in 83% crude yield. To obtain directly the desilylated alcohols **7**, one more equivalent of BF_3 was necessary.[8c] The reaction with 1-phenylsulfanylbutadiene gave cycloadduct **8** as a mixture of endo and exo isomers (ratio 7:1), in 85% crude yield. The endo/exo ratios were determined by ^1H NMR of the crude mixtures. According to previous results obtained in our group,[8c] we assumed that the major isomers of **7** and **8** were formed according to the endo rules.

Cycloadduct **5a** was then submitted to protodesulfanylation, reduction, and oxidation reactions to obtain cyclic sulfoxide **11**, which is a known intermediate used in the synthesis of Aprikalim (Scheme 5).[1c] First, we tried to reduce **5a** into the corresponding saturated thiapyran using $Pd(OH)_2$ as catalyst in MeOH, under 20 bar, for 48 h. We noticed that under these conditions **5a** was partially (20%) isomerized into *iso*-**5a** (Scheme 5). Because the methylsulfanyl group can facilitate the Pd-catalyzed isomerization, we decided to protodesulfanylate **5a** before reduction and to reduce the resulting unsaturated thiapyran.

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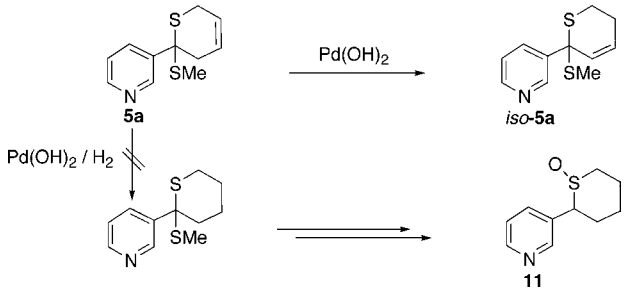
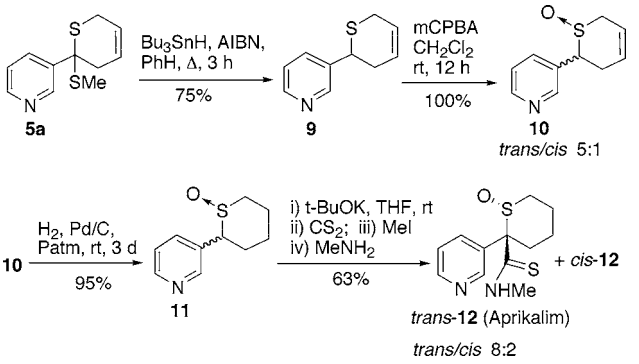
Scheme 5. Reduction of **5a** under Pd Catalysis



The desulfanylation of **5a** was done under radical conditions, using the Bu_3SnH/AIBN couple.[8a] Under these conditions, the methylsulfanyl group was cleaved selectively to give the expected compound **9** in 75% yield. However, all our attempts to reduce the double bond of the unsaturated thiapyran **9** using Pd/C in MeOH under high pressure (up to 20 bar) failed; only the starting material was recovered. We supposed that this result was due to the poisoning of the Pd catalyst by the sulfur atom. To avoid this possibility, we oxidized compound **9** by using *meta*-chloroperbenzoic acid (mCPBA) into the corresponding sulfoxide **10**, which was obtained as a 5:1 mixture of trans/cis isomers (Scheme 6).

Scheme 6. Transformation of Cycloadduct **5a** into Sulfoxide **11** and Access to Aprikalim



Then, sulfoxide **10** was successfully hydrogenated using Pd/C in MeOH, under atmospheric pressure, for 3 days, leading to the saturated sulfoxide **11**, of which the trans and cis isomers were separated by chromatography. The spectral data of **11** are in agreement with the literature data,[1c] and the overall yield was 56% starting from **1a**.

Starting from sulfoxide **11**, we reproduced the sequence described in the literature[1c] to accede to Aprikalim **12**: deprotonation in α-position to the sulfinyl group by *t*-BuOK, addition of carbon disulfide and methylation to obtain the dithioester intermediate, and, then, reaction of the dithioester with methylamine. NMR data of the obtained compound **12** were in agreement with those of the literature and showed the presence of Aprikalim (trans isomer) together with the cis isomer (trans/cis 8:2).

In conclusion, we have shown that pyridinedithioesters can be used as efficient heterodienophiles. The thiocarbonyl group of these dithioesters was activated by increasing the electron-withdrawing character of the pyridine heterocycle by complexation of the nitrogen atom with a Lewis acid (BF_3), by protonation, or by oxidation. Using the hetero-Diels−Alder reaction with the protonated 3-pyridinedithioester and the butadiene as the key step, we synthesized Aprikalim in racemic form in eight steps, starting from commercially available 3-picolyl chloride[12] (overall yield = 23%). This methodology should allow easy modulation of the Aprikalim structure, on the pyridine moiety or on the thiapyran heterocycle (using various dithioesters or dienes, or modifying the cycloadduct), leading to a large variety of new analogues of Aprikalim. We are currently working on this topic.

(12) Pyridinedithioester **1a** was synthesized by the procedure described in ref 10, starting from 3-picolyl chloride, in two steps and in 80% overall yield.

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Supporting Information Available: Spectral data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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