Preparation of Thiochromans *via* Thermal Cyclization

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Formation of the thiochroman ring system is achieved by a two step synthesis that involves heating 3-thiophenyl-1-propanols or 4-thiophenyl-2-butanols in toluene with catalytic amounts of *p*-toluenesulfonic acid. The propanols are made by the addition of sulfur stabilized carbanions to styrene oxide, ethylene oxide, propylene oxide, and isobutylene oxide. The carbanions are generated by treatment of either benzyl phenyl sulfide or thioanisole with butyllithium. The effect of substitution at the 1 and 3 positions of the propanols on the reaction yields is discussed. The mechanism of the reaction apparently involves intramolecular electrophilic aromatic substitution rather than a Claisen or thio-Claisen rearrangement.

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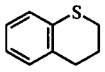
The thiochromans (3,4-dihydro-2*H*-1-benzothiopyrans, **1**) are a useful class of sulfur heterocycles. Derivatives of **1** have been used in industry as fuel additives, resins, dyes, solvent clathrates, and in uranium extractions [1]. Biologically important derivatives of **1** include diuretics, antiinflamatory agents, antipyretics, analgesics, antidepressants, antihypertensives, agents against angina pains, oral infertility agents, antiamebics, antimicrobials, virucides, insecticides, acaricides, and antiedemics [1].



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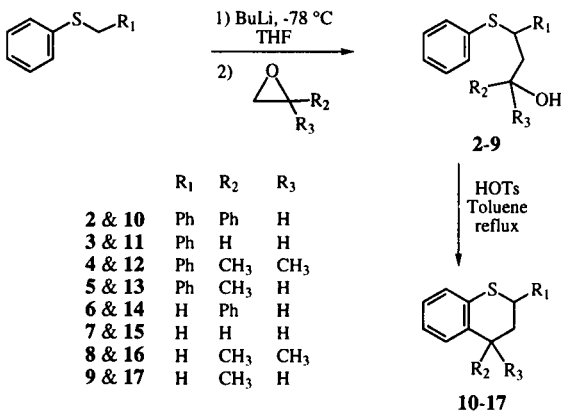
Not surprisingly, several syntheses have been reported for the thiochromans [2-13]. Thiochromans have been made by: A) intramolecular electrophilic aromatic substitution of aryl thioethers that have an electrophilic functional group (carbonyl [1,2], chlorine [3,4], thioacetal [5], and alcohol [6,7]) tethered to the sulfur atom, B) thioclaisen rearrangement of allyl phenyl sulfides [1,7-9], C) reduction (H_2/catalyst, Wolff-Kishner, or Clemenson) of the corresponding thiochromones (4*H*-1-benzothiopyran-4-ones) and thiochromanones (2,3-dihydro-4*H*-1-benzothiopyran-4-ones) [1,10,11], D) Diels-Alder cycloaddition [12,13], and E) a thermal rearrangement possibly involving S_N2 displacement of chlorine by a thiol [1]. Thiochromans are also isolated from petroleum [1].

Thiochromans have been used as a synthon for the addition of methyl and phenyl groups across double bonds. This was achieved by Ra-Nickel reduction of derivatives of **1** after cyclization with an olefin and proved useful in the synthesis of sesquiterpenoids [3,4].

Previously we reported that benzyl phenyl sulfides react upon uv irradiation to give benzyl and thiophenyl radicals which then rearrange to a variety of compounds [14-16]. An analogous thermal cleavage occurs only at high temperatures (above 200 °C) [17-19]. During an attempt to synthesize 1,3-diphenyl-3-thiophenylpropene by dehydration of 1,3-diphenyl-3-thiophenyl-1-propanol, we found that 2,4-diphenylthiochroman [20] was formed in 95% overall yield. Only the *cis* diastereomer was formed. This ring forming reaction was surprising to us because sulfur is generally not a good substituent for electrophilic aromatic substitutions. For example, 4-methylthioanisole preferentially undergoes electrophilic deuteration ortho to the methyl group [21]. Additionally, the σ_p value for -SCH_3 is 0.00 [22]. In this paper we report our investigation of the mechanism and generality of this type of thiochroman synthesis.

The first step in our synthesis (see Equation 1) involves addition of a methyl or benzyl phenyl sulfide anion to an epoxide. Both sulfur stabilized anions are bright yellow. Deprotonation of methyl phenyl sulfide occurs best with fresh *tert*-butyl lithium, but *n*-butyl lithium is sufficiently



	R_1	R_2	R_3
2 & 10	Ph	Ph	H
3 & 11	Ph	H	H
4 & 12	Ph	CH_3	CH_3
5 & 13	Ph	CH_3	H
6 & 14	H	Ph	H
7 & 15	H	H	H
8 & 16	H	CH_3	CH_3
9 & 17	H	CH_3	H

Equation 1.

basic to form the benzyl phenyl sulfide anion. Addition of the epoxide to the carbanion is highly exothermic in all cases and must be done dropwise at 0 °C.

Cyclization of alcohols **2-9** was attempted by refluxing a solution of each alcohol with a catalytic amount of *p*-toluenesulfonic acid in toluene. This resulted in good to excellent yields of **10**, **14**, and **16**. Thiochromans **13** and **17** were formed in lower yields. Thiochromans **11**, **15**, and surprisingly **12** did not form under the reaction conditions.

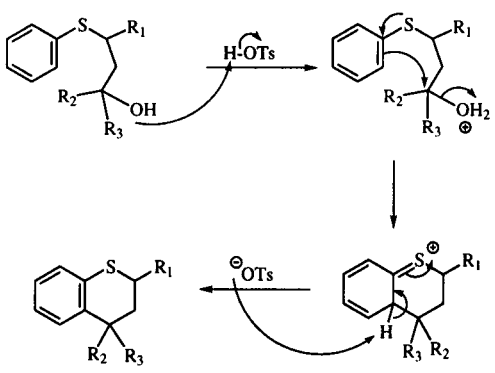
Table 1

Yields of Alcohol and Thiochroman Products

Alcohol	Alcohol Yields [a]	Thiochroman	Thiochroman Yields [b]
2	100%	**10**	100% (95%)
3	86%	**11**	0%
4	100%	**12**	trace amount
5	91%	**13**	20%
6	50%	**14**	70% (34%)
7	29%	**15**	0%
8	79%	**16**	97% (78%)
9	63%	**17**	32%

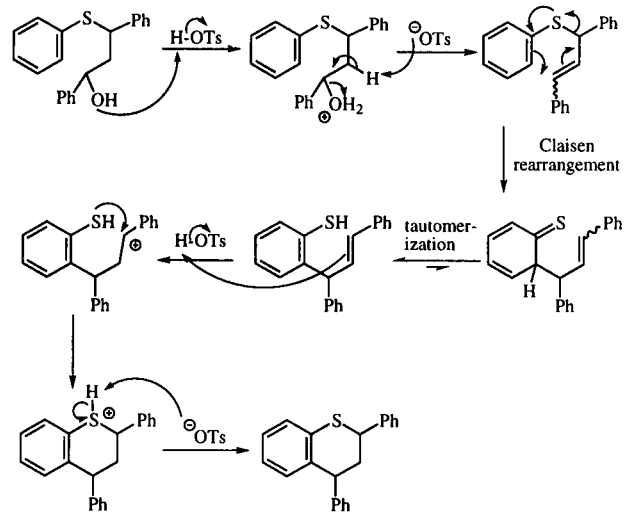
[a] All are purified yields except **2** & **4**; [b] For mechanistic comparison, all are crude yields determined by nmr (purified yields that could be determined are listed in parentheses).

The mechanism for the cyclization is presumably an electrophilic aromatic substitution. The alcohol would be initially protonated by the acid, water then acts as a leaving group which is replaced by the phenyl ring. The involvement of the intermediate carbocation is implicated by the observation that the primary alcohols **3** and **7** do not undergo cyclization. Rearomatization occurs after the thiopyran ring is formed (Equation 2). Although toluene solvent is more electron rich, the intramolecular cyclization is entropically favored. Interestingly, the methyne next to the sulfur atom of **2** does not activate the phenyl ring attached to it sufficiently to drive electrophilic aromatic substitution on that ring, which would result in a fused five-membered ring. This is presumably due to the energy difference between five- and six-membered rings and the thermodynamic reaction conditions.

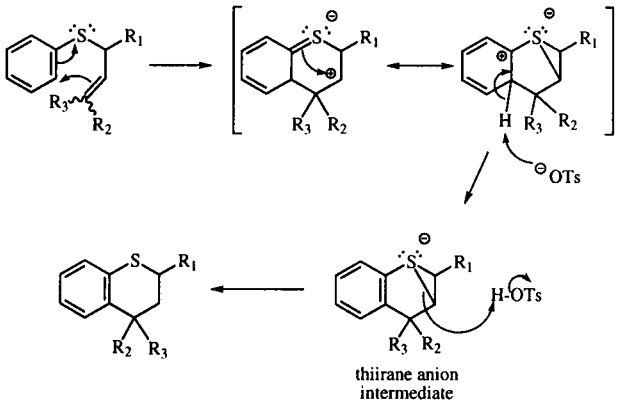


Equation 2. Electrophilic Aromatic Substitution.

Because **11** and **15** are not formed, while **10**, **14**, and **16** are, a typical Claisen cyclization is unlikely (see Equation 3). A third mechanistic consideration is the proposed thio-Claisen cyclization which is significantly different than the Claisen and involves a hypervalent sulfur (see Equation 4) [23]. This mechanism is not likely for two reasons. First, as with the Claisen, groups other than H at R_2 and R_3 should hinder the reaction. Second, the thiirane intermediate should give rise to both five- and six-membered rings (thiocoumarans and thiochromans respectively) for compound **14** and **16**, which is not observed [23].



Equation 3. Claisen.



Equation 4. thio-Claisen.

The lack of thiochroman **12** in the cyclization of alcohol **4** may be explained by steric interactions and/or by the weakness of the benzyl-sulfur bond. Compounds **12** and **16** both have an unfavorable 1,3-diaxial-like interaction between a methyl group and a hydrogen adjacent to the sulfur. In the case of **12**, the weaker benzyl-sulfur bond may be cleaved under the acidic reaction conditions to relieve this strain (forming a benzyl cation and a thiol). The bond dissociation energy (BDE) for the benzyl-sulfur bond is about 53 kcal/mol [24,25]. In the case of **16**, which is stable under the reaction conditions, the methylene-sulfur bond energy is closer to 61 kcal/mol [26]. These BDE values are for homolytic bond cleavage. The heterolytic BDE values in acid, which are unknown, would likely have even greater differences. No stabilized carbocation could be formed by acidic cleavage of **16**.

In conclusion, alcohols **2-9** are efficiently formed by addition of sulfur stabilized carbanions to epoxides. If the alcohol is sufficiently substituted, it may undergo thermal cyclization to thiochromans. Thus, this two step procedure is a useful synthetic approach to the general synthesis of thiochromans.

Acknowledgements.

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EXPERIMENTAL

General Procedures.

Benzyl phenyl sulfide, thioanisole, *n*-BuLi, *t*-BuLi, propylene oxide, styrene oxide, and isobutylene oxide were purchased from either Aldrich or Lancaster and used without further purification. THF was distilled from benzophenone ketyl.

General Synthesis of Alcohols **2-9**.

To 1.0 equivalent of benzyl phenyl sulfide or thioanisole in THF at -78 °C was added 1.1 equivalents of *n*-BuLi or *t*-BuLi. Both carbanions were bright orange-yellow opaque slurries. However, when *n*-BuLi was added to thioanisole, only a light pale yellow resulted which was indicative of incomplete deprotonation. The mixture was stirred for 0.5 hour at -78 °C and then 1.2 equivalents of epoxide was added dropwise. The reaction was allowed to warm to room temperature and stirred for about 12 hours before quenching with 10% HCl. The reaction mixture was then washed with bicarbonate (2x), water, and brine before drying with anhydrous sodium sulfate and concentrating *in vacuo*. If the yield of an alcohol was not quantitative, it was purified prior to cyclization.

Synthesis of 1,3-Diphenyl-3-thiophenyl-1-propanol (**2**).

To 0.90 g of benzyl phenyl sulfide dissolved in 25 ml of THF at -78 °C was added 2.3 ml of 2 *M* *n*-BuLi in hexanes. Then 0.64 ml of styrene oxide was added dropwise over about 2 minutes. The crude yield of diastereomeric alcohols was quantitative. The spectral data was consistent with the literature values [27].

Synthesis of 3-Phenyl-3-thiophenyl-1-propanol (**3**).

To 1.04 g of benzyl phenyl sulfide dissolved in 23 ml of THF at -78 °C was added 2.8 ml of 2 *M* *n*-BuLi in hexanes. Then 0.6 ml of ethylene oxide was added dropwise over 1 minute while keeping the syringe cooled with ice. Some of the ethylene oxide evaporated during the addition. The reaction was stirred in an ice bath for about 1.5 hours and then stirred at room temperature overnight before quenching with 10% HCl. Following the workup, TLC (10% EtOAc in pentane) of the crude reaction mixture showed a product with an R_f of about 0.1 in addition to unreacted starting material. Purification by column chromatography (10% EtOAc in pentane and slowly increasing the percentage of EtOAc) gave 1.10 g of purified **3** (4.50 mmoles, 86% yield). The spectral data were consistent with the literature [28].

Synthesis of 2-Methyl-4-phenyl-4-thiophenyl-2-butanol (**4**).

To 5.03 g of benzyl phenyl sulfide dissolved in 10 ml of THF at -78 °C was added 13.7 ml of 2 *M* *n*-BuLi in hexanes. Then 3.0 ml of isobutylene oxide was added dropwise over 2 minutes. The reaction was allowed to slowly warm to room temperature and was stirred overnight before quenching with 10% HCl. Analysis by tlc (10% EtOAc in pentane) indicated a product with an R_f of less than 0.1. The crude material was at least 95% pure as determined by nmr. The yield of crude product was quantitative. Compound **4** is a new compound: ^{1}H nmr ($CDCl_3$) δ (ppm) 7.15-7.30 (m, 10H, 2 x Ph.), 4.40 (t, J = 8 Hz, 1H, CH), 2.22 (d, J = 8 Hz, 2H, CH_2), 1.9 (bs, 1H, OH), 1.23 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); ^{13}C nmr ($CDCl_3$) δ (ppm) 29.0, 31.0, 48.0, 50.0, 72.0, 127.0, 127.4, 127.8, 128.3, 128.6, 132.8, 134.2, 142.7; ir (neat) 3396.9, 3058.9, 2698.9, 1582.5, 1479.3, 1438.2, 1206.7, 1136.6, 745.6, 695.9 cm^{-1}.

Anal. Calcd. for C, 74.95; H, 7.40; S, 11.77. Found: C, 75.00; H, 7.54; S, 11.56.

Synthesis of 4-Phenyl-4-thiophenyl-2-butanol (**5**).

To 5.22 g of benzyl phenyl sulfide dissolved in 40 ml of THF at -78 °C was added 13.8 ml of 2 *M* *n*-BuLi in hexanes. Then 2.4 ml of propylene oxide was added dropwise over about 2 minutes. The reaction was allowed to slowly warm to room temperature and was stirred overnight before quenching with 10% HCl. Analysis by tlc (10% EtOAc in pentane) showed a product with an R_f of 0.18. The yield of crude product was 91%. A portion of this product was distilled at 130 °C and 0.50 torr to give the desired pure product, which is mixture of two diastereomers (47% yield). The spectral data were consistent with the literature values [29].

Synthesis of 1-Phenyl-3-thiophenyl-1-propanol (**6**).

To 2.0 ml of thioanisole dissolved in 10 ml of THF at -78 °C was added 17.0 ml of 1.5 *M* *t*-BuLi in hexanes. Then 2.84 ml of styrene oxide was added dropwise over several minutes. Upon initial addition of epoxide the reaction fumed and turned dark brown at the point of contact between the drop of epoxide and the slurry. After addition of epoxide the reaction was allowed to slowly warm to room temperature and was stirred overnight (solution turned a clear orange color) before quenching with 10% HCl. After workup, the yield of crude product appears to be about 50%

(based on the integration ratio between starting material and product in the ^1H nmr). A portion of this product was distilled at 225 °C and 0.45 torr to give the desired pure product, which is a highly viscous clear liquid (28% yield). The spectral data were consistent with the literature values [29].

Synthesis of 3-Thiophenyl-1-propanol (**7**).

To 5.0 ml (2.0 equivalents) of thioanisole dissolved in 22 ml of THF at -78 °C was added 10.9 ml of 2.0 *M* *n*-BuLi (1.0 equivalent) in hexanes. The solution was colored light yellow. The mixture was stirred for 1 hour at -78 °C and then 0.6 ml (large excess) of ethylene oxide was added dropwise over 1 minute while keeping the syringe cooled with ice. Some of the ethylene oxide evaporated during the addition. After addition of epoxide the reaction was allowed to slowly warm to room temperature and was stirred overnight (turned cloudy yellow) before quenching with 10% HCl. After workup and distillation of the unreacted starting material, the yield of alcohol **7** was 29%. The spectral data was consistent with the literature [30].

Synthesis of 2-Methyl-4-thiophenyl-2-butanol (**8**).

To 0.6 ml of thioanisole dissolved in 20 ml of THF at -78 °C was added 2.8 ml of 2.0 *M* *n*-BuLi in hexanes. Then 0.59 ml of isobutylene oxide was added dropwise over several minutes. After addition of epoxide the reaction was allowed to slowly warm to room temperature and was stirred overnight before quenching with 10% HCl. After workup the tlc (10% EtOAc in pentane) showed a product with an R_f of 0.1. The crude product was purified by column chromatography (10% EtOAc in pentane and slowly increasing the percentage of EtOAc) to give 0.80 g (4.1 mmoles, 79% yield) of purified alcohol **8**. The spectral data were consistent with the literature values [7].

Synthesis of 4-Thiophenyl-2-butanol (**9**).

To 2.0 ml of thioanisole dissolved in 10 ml of THF at -78 °C was added 17.0 ml of 1.5 *M* *t*-BuLi in hexanes. Then 2.53 ml of propylene oxide was added dropwise over several minutes. After addition of epoxide the reaction was allowed to slowly warm to room temperature and was stirred overnight (solution turned a clear light yellow then brownish-yellow color) before quenching with 10% HCl. After workup the yield of crude product was determined to be 63% (based on the integration ratio between starting material and product in the ^1H nmr). A portion of this product was distilled from 145-160 °C and 0.40 torr to give the desired pure product, which is a viscous liquid (58% yield). The data was consistent with the literature [27].

General Synthesis of Thiochromans **10-17**.

To alcohols **2** through **9** in toluene was added a catalytic amount of *p*-toluenesulfonic acid (TsOH). The reaction was refluxed for about 12 hours then washed with bicarbonate (2x), water, and brine, and then dried with anhydrous sodium sulfate before concentrating *in vacuo*.

Synthesis of 3,4-Dihydro-2,4-diphenyl-2*H*-1-benzothiopyran (**10**).

To 1.6 g of crude alcohol **2** in about 50 ml toluene was added 0.37 g TsOH. The reaction was fitted with a Dean Stark Trap, refluxed for 12 hours and stopped. After workup, the crude yield was quantitative. A first portion, purified by chromatography (pentane, R_f = 0.2), yielded 40% pure material. A second portion, purified by washing the crude product with pentane and recrystallizing from diethyl ether, yielded 55% pure off-white crystals in the first batch (mp 129-132 °C) [31]; ^1H nmr ($CDCl_3$) δ (ppm) 7.10-7.40 (m, 10H, 2 x Ph.), 7.10 (d, *J* = 8 Hz, 1H), 7.00 (t, *J* = 8 Hz, 1H), 6.80 (t, *J* = 8 Hz, 1H), 6.65 (d, *J* = 8 Hz, 1H), 4.60 (m, 1H, CH), 4.20 (m, 1H, CH), 2.50 (m, 2H, CH_2); ^{13}C nmr ($CDCl_3$) δ 145.6, 141.7, 137.4, 135.2, 130.6, 129.3, 128.4, 128.1, 127.3, 127.1, 126.6, 124.8, 48.0, 47.0, 42.0. ir (KBr) 2910.6, 1492.6, 1469.2, 1452.1, 1429.7, 1049.6, 788.6, 760.1, 701.2 cm^{-1}; ms (M = 302) 301, 209, 196 m/z. The crystal structure of **10** was solved and verified that only the *cis*-diastereomer was formed.

Attempted Synthesis of 3,4-Dihydro-2-phenyl-2*H*-1-benzothiopyran (**11**).

To 3.19 g of alcohol **3** in 35 ml toluene was added 0.99 g TsOH. The reaction was fitted with a Dean Stark Trap, refluxed for about 11 hours and stopped. The reaction color turned cherry-red as the reflux began and then became very dark red. After reflux was complete, the color was brownish-red. After the workup there was no indication of the starting material and no thiochroman was obtained.

Attempted Synthesis of 3,4-Dihydro-4,4-dimethyl-2-phenyl-2*H*-1-benzothiopyran (**12**).

To 0.54 g of alcohol **4** in 20 ml toluene was added 0.167 g TsOH. The reaction was fitted with a Dean Stark Trap, refluxed for 10 hours and stopped. The reaction color turned light yellow as the reflux began. After reflux was complete, the color was tan. Spectral analysis of the crude reaction mixture after workup indicated that almost all of the starting alcohol reacted; however, the desired product was not apparent in the mixture. Based on careful analysis of the aromatic region of the spectrum from 6.5-7.0 ppm (aromatic H for a fused thiophenyl ring) a trace amount of desired thiochroman **12** appears to have formed.

Synthesis of 3,4-Dihydro-4-methyl-2-phenyl-2*H*-1-benzothiopyran (**13**).

To 0.511 g of alcohol **5** in 20 ml toluene was added 0.154 g TsOH. The reaction was fitted with a Dean Stark Trap, refluxed for 10 hours and stopped. The reaction color turned purple as the reflux began. During the refluxing the color changed to reddish-brown, then finally to brown. After workup, the spectral analysis of the crude reaction mixture indicated that only about 20% of **13** formed at 100% conversion. When the reaction was stopped at about 70% conversion, the yield was approximately 30%. Attempts to purify thiochroman **13** by bulb-to-bulb distillation and chromatography were unsuccessful. The compound decomposes on silica and at high temperatures. However, the spectral data of thiochroman **13** in the crude material was consistent with the literature value [32]. Compound **13** is actually a mixture of two diastereomers (approximately 3:2 based on ^1H nmr integrations).

Synthesis of 3,4-Dihydro-4-phenyl-2*H*-1-benzothiopyran (**14**).

To 0.203 g of alcohol **6** in about 15 ml toluene was added 0.070 g TsOH. The reaction was fitted with a reflux condenser and refluxed for 5 hours. After workup, the crude yield of thiochroman **14** was 70% (based on ^1H nmr integration ratios of the crude product mixture). The product was distilled *via* kugelrohr at 210-215 °C and 0.50 torr to give a highly viscous clear liquid in 34% yield. At the high temperatures associated with

this distillation, some of the product may have decomposed. The spectral data for this compound were consistent with the literature values [33].

Attempted Synthesis of 3,4-Dihydro-2*H*-1-benzothiopyran (**15**).

To 1.02 g of alcohol **7** in about 35 ml toluene was added 0.509 g TsOH. The reaction was fitted with a Dean Stark Trap and refluxed for 11.5 hours. The reaction color turned from yellow to dark reddish-brown during that time. After workup, analysis of the crude reaction mixture by ^{1}H nmr indicated that the reaction mixture was mostly unreacted alcohol **7**.

Synthesis of 3,4-Dihydro-4,4-dimethyl-2*H*-1-benzothiopyran (**16**).

To 0.395 g of alcohol **8** in about 20 ml toluene was added 0.162 g TsOH. The reaction was fitted with a Dean Stark Trap and refluxed for 11.5 hours. The reaction color turned tan after a few hours of reflux. After workup, analysis of the crude reaction mixture by ^{1}H nmr indicated that the reaction mixture (dark oil) was fairly pure thiochroman **16** obtained in a crude yield of 97%. The product was further purified by kugelrohr distillation at 112 °C and 0.50 torr to give the pure product as a faint yellow liquid in 78% yield which was consistent with the literature data [7].

Synthesis of 3,4-Dihydro-4-methyl-2*H*-1-benzothiopyran (**17**).

To 0.094 g of alcohol **9** in about 10 ml toluene was added about 0.070 g TsOH. The reaction was fitted with a reflux condenser and refluxed for about 5 hours. After workup, analysis of the crude reaction mixture by ^{1}H nmr indicated that 32% of thiochroman **17** formed. The spectral data were consistent with the literature values [34].

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