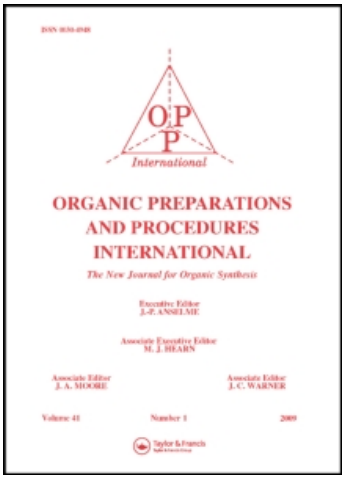

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF ISOTHIOCHROMANS. A REVIEW

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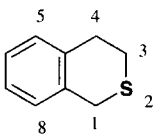
INTRODUCTION

According to *Chemical Abstracts*, the name of the family of compounds to be reviewed is 3,4-dihydro-1*H*-2-benzothiopyran although some of the early literature referred to these compounds as benzothiapyrans. Recently, more publications have used the name of isothiochroman. Throughout this review, both isothiochroman and benzothiopyran will be used interchangeably.



Isothiochromans constitute a subcategory of heterocyclic compounds. Although sulfur-containing heterocycles have been known for a long time, interest in benzothiopyrans has not grown as much as that in the benzopyran system. This probably reflects the wide availability of diverse 6-membered oxygen heterocyclic natural products in comparison with the near absence of naturally occurring sulfur containing analogs.[1]

Recently, interest in seeking biologically active compounds has prompted increased studies in isothiochroman derivatives. Isothiochromans are structural analogs (bioisosteres) of many bicyclic systems including chroman, isochroman, tetrahydroisoquinoline, tetrahydroquinoline, thiochroman, and tetralin. These bicyclic derivatives can be used interchangeably as the basic structure to improve the desired biological activity.[2] In addition, 1-aminoalkylisothiochromans have been synthesized and used as conformationally restricted analogs of phenylethylamines, which are of interest as analogs of neurotransmitters.[3] The increasing number of publications and patents during the recent years indicates the undoubted value of isothiochroman system in the studies of structure and activity relationships (SAR). In spite of the considerable interest in the isothiochroman derivatives, the chemistry and reactivity of this class of heterocyclic compounds have been scarcely reviewed in the literature.[4] The present review surveys the *de novo* synthetic methods, classified according to the reaction type of the heterocyclic ring closure. It also covers the chemical reactivity of isothiochroman derivatives, which is discussed in terms of reaction sites on the isothiochroman system.

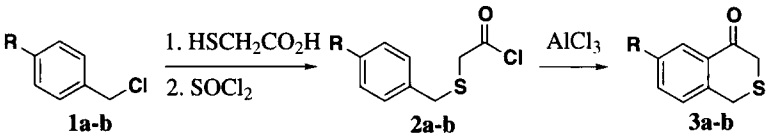
I. SYNTHESIS OF ISOTHIOCHROMANS

There are few naturally occurring benzothiopyran derivatives.[1] Isothiochromans are only available through *de novo* synthetic approaches.

1. Intramolecular Friedel-Crafts Reactions

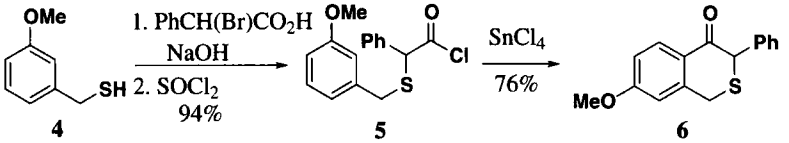
The bicyclic skeleton of isothiochroman is readily obtained from suitably functionalized acyclic precursors using intramolecular Friedel-Crafts reactions. This approach was discovered a long time ago[4] and has been widely used for the synthesis of isothiochroman derivatives.

A variety of acids can mediate the Friedel-Crafts cyclization. Aluminum chloride has been known for a long time to promote the Friedel-Crafts ring closure of acyl chlorides **2a-b** to isothiochroman-4-one **3a-b** (Eq. 1).[5,6] The search for potential antifertility agents led to the preparation of 3-phenyl isothiochroman-4-one **6** by use of $SnCl_4$ as Lewis acid.[7a] The Friedel-Crafts acylation occurs exclusively at the *para*-position of the methoxy group to afford a single regioisomer (Eq. 2).[7]



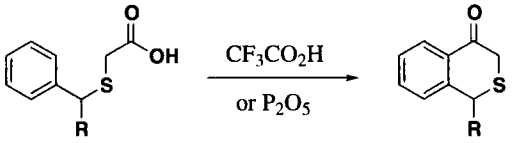
1a-b **2a-b** **3a-b** (1)

a) R = H (52%) b) R = *t*-Bu (unspecified yield)



4 **5** **6** (2)

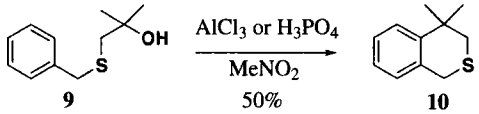
Isothiochroman-4-one may also be obtained directly from the intramolecular Friedel-Crafts reaction of the corresponding carboxylic acids. For example, the acid **7a-b** are converted to isothiochromanones **8a-b** in good yields by either trifluoroacetic acid[8] or phosphorus pentoxide[9] as catalyst (Eq. 3).



7a-b **8a-b** (3)

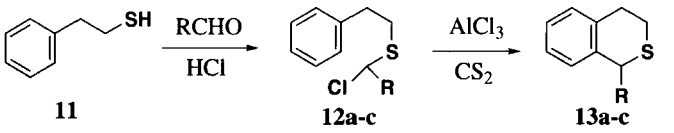
a) R = Ph (52%) TFA, CH_2Cl_2, rt, 0.5h b) R = H (80%) P_2O_5, celite, PhH, reflux

Tertiary alcohols also serve as precursors for Friedel-Crafts cyclization. Treatment of **9** with $AlCl_3$ or H_3PO_4 gives isothiochroman **10** (Eq. 4).[10] α-Chlorosulfides **12a-c**, which are obtained from



9 **10** (4)

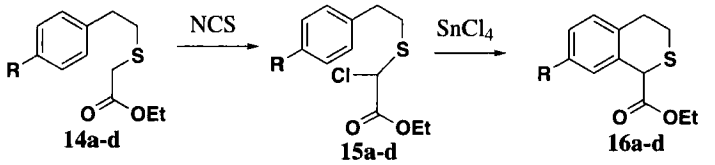
the thiol **11** by treatment with aliphatic aldehydes in the presence of HCl, can be converted to isothiochromans **13a-c** in moderate yields through an intramolecular Friedel-Crafts reaction (Eq. 5).[11]



11 12a-c 13a-c (5)

a) R = H (65%) b) R = Me (40%) c) R = Et (30%)

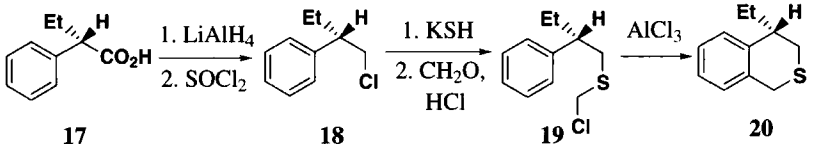
Ishibashi *et al.* reported a synthesis of isothiochromans **16a-d** using $SnCl_4$ to promote intramolecular cyclization of α-chlorosulfides **15a-d**, which are readily available by chlorination of sulfides **14a-d** using *N*-chlorosuccinimide (NCS). The isothiochroman derivatives **16a-d** thus obtained were used in the SAR studies of antiinflammatory agents (Eq. 6).[12]



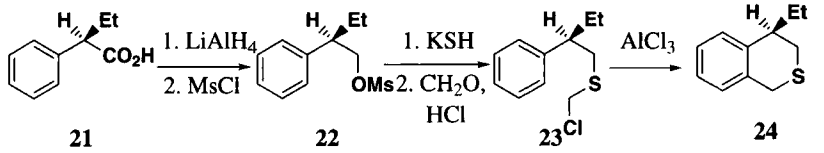
14a-d 15a-d 16a-d (6)

a) R = H (87%) b) R = CH_2CHMe_2 (94%) c) R = OPh (67%) d) R = SPh (39%)

In order to study the conformational changes of isothiochromans by introduction of an alkyl substituent at the C-4 position, both enantiomers, (S)-(+)-4-ethylisothiochroman **20** and (R)-(-)-4-ethylisothiochroman **24** were synthesized by Biscarini *et al.* using intramolecular Friedel-Crafts cyclization of the corresponding α-chlorosulfides **19** and **23**, respectively (Eq. 7).[13,14]

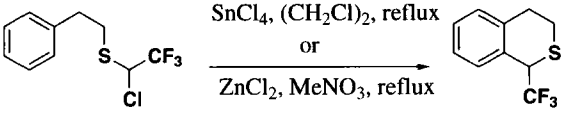


17 18 19 20



21 22 23 24 (7)

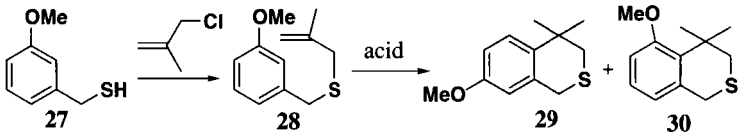
Both $SnCl_4$ and $ZnCl_2$ can promote the C-C bond formation as in the reaction of the α-chlorosulfide **25** to give 1-trifluoromethylisothiochroman **26** (Eq. 8).[15]



25 26 (8)

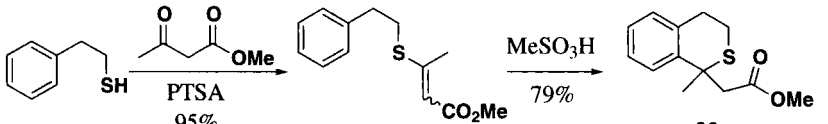
Another method to synthesize isothiochroman system *via* the intramolecular Friedel-Crafts cyclization approach is to use an olefinic precursor as in the synthesis of analgesic compounds containing an isothiochroman moiety.[16] A variety of acids were investigated for the cyclization with

the acyclic olefin **28**. They all could effect the Friedel-Crafts cyclization although different ratios of the two possible regioisomers and different yields of these products were obtained (Eq. 9). In the presence of acid, a vinyl alkyl sulfide can also undergo C-C bond formation reaction with an aromatic substrate in an intramolecular fashion to give substituted isothiochroman as illustrated by the synthesis of 1,1-disubstituted isothiochroman **33** shown below (Eq. 10).[17]



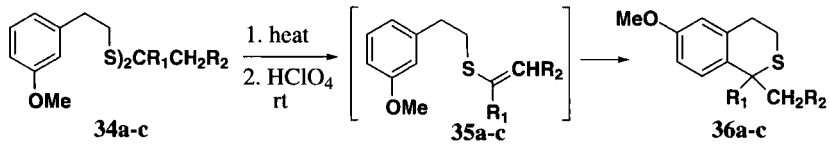
27 28 29 30 (9)

Acid	Ratio (**29**:**30**)	Yield (%)
H_2SO_4, 50°	2 : 1	100
H_2SO_4, H_3PO_4 (1:1), rt	**29** only	48
$BF_3.Et_2O$, rt	2 : 1	80
$AlCl_3$, 0°	2 : 1	30
TsOH, reflux	2 : 1	90
PPA	**29** only	25



31 32 33 (10)

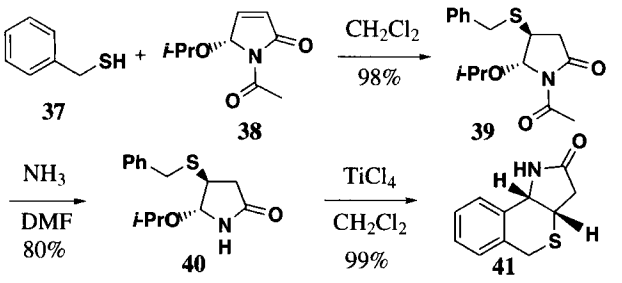
de Waard and co-workers reported an interesting method for the preparation of isothiochromans starting from thioacetals or thioketals.[18] For example, thermal pyrolysis of compounds **34a-c**, generated vinyl sulfide intermediates **35a-c**, that underwent intramolecular cyclization upon the addition of $HClO_4$ to afford isothiochromans **36a-c** in a quantitative yield. The cyclization reaction is regioselective with the formation of exclusively one regioisomer (Eq. 11). Alternatively, the reactions could also be accomplished by using iodomethane or boron trifluoride diethyl ether to assist the formation of the vinyl sulfide intermediate.



34a-c 35a-c 36a-c (11)

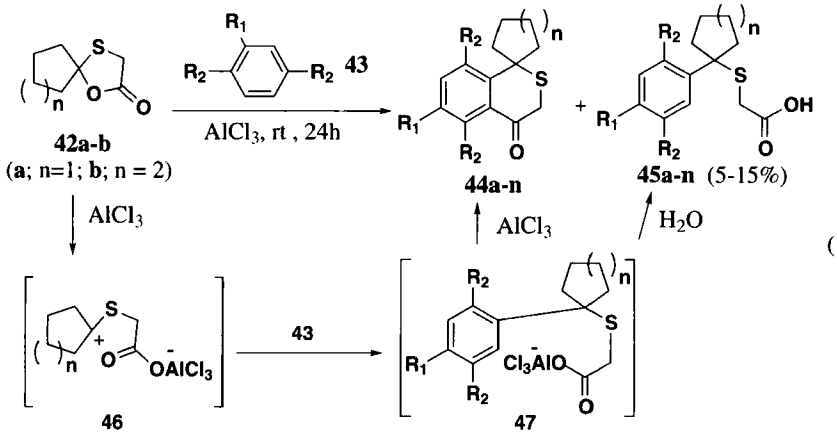
a) R_1 = Me, R_2 = H b) $R_1 = R_2$ = -$(CH_2)_4$- c) $R_1 = R_2$ = Me

Conjugate addition of benzyl mercaptan **37** to (R)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one **38** was reported to proceed quantitatively and stereoselectively.[19] Deacylation of conjugated product **39** by treatment with ammonia in DMF yielded **40** in 80% yield. This lactam was subjected to Friedel-Crafts cyclization conditions employing $TiCl_4$ as Lewis acid. The isothiochroman based tricyclic product **41** was obtained as an optically pure isomer in virtually quantitative yield (Eq. 12).[19]



(12)

The reaction of 1-oxa-4-thiaspiro[4,4]nonan-2-one (**42a**) or 1-oxa-4-thiaspiro[4,5]decan-2-one (**42b**) with aromatic substrates **43** under the catalytic action of $AlCl_3$ afforded a variety of spiro[cycloalkane-1,1'-isothiochroman]-4'-one derivatives **44a-n** as major products in yields ranging from 50 to 80%.[20] The reaction is proposed to proceed through a tandem inter- and intramolecular Friedel Crafts reactions as shown below (Eq. 13).

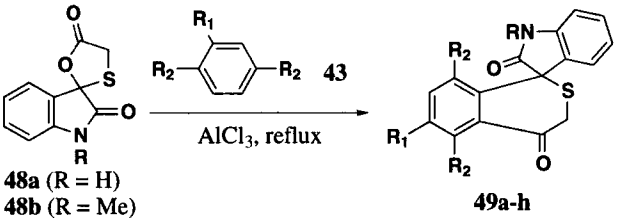


(13)

a) $R_1 = R_2 = H$, n = 1 (60%)
b) $R_1 = Me$, $R_2 = H$, n = 1 (78%)
c) $R_1 = H$, $R_2 = Me$, n = 1 (80%)
d) $R_1 = Br$, $R_2 = H$, n =1 (50%)
e) $R_1 = Cl$, $R_2 = Me$, n = 1 (50%))
f) $R_1 = OMe$, $R_2 = H$, n = 1 (55%)
g) $R_1 = Ph$, $R_2 = H$, n = 1 (76%)
h) $R_1 = R_2 = H$, n = 2 (70%)
i) $R_1 = Me$, $R_2 = H$, n = 2 (75%)
j) $R_1 = H$, $R_2 = Me$, n = 2 (80%)
k) $R_1 = Br$, $R_2 = H$, n = 2 (55%)
l) $R_1 = Cl$, $R_2 = H$, n = 2 (50%)
m) $R_1 = OMe$, $R_2 = H$, n = 2 (70%)
n) $R_1 = Ph$, $R_2 = H$, n = 2 (70%)

Similar chemistry has been extended to a different spirocyclic system. The reaction of spiro[indoline-3,2'[1,3]oxathiolane-2,5'-dione **48a-b** with substituted benzene **43** in the presence of $AlCl_3$ under reflux gives spiroindoline isothiochroman derivatives **49a-h** in good yields (Eq. 14).[21]

Another interesting method for the preparation of isothiochroman involves the cyclization of acyl chloride **50** in the presence of $AlCl_3$ to form isothiochroman **51** in very good yield with concomitant loss of carbon monoxide (Eq. 15).[22]

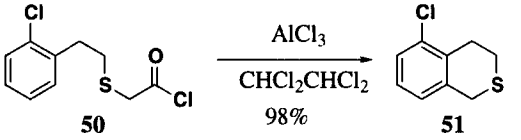


48a (R = H)
48b (R = Me)

49a-h

(14)

a) R = H, R_1 = R_2 = H (70%) b) R = H, R_1 = Me, R_2 = H (69%)
c) R = H, R_1 = OMe, R_2 = H (67%) d) R = H, R_1 = H, R_2 = Me (65%)
e) R = Me, R_1 = R_2 = H (60%) f) R = Me, R_1 = Me, R_2 = H (65%)
g) R = Me, R_1 = OMe, R_2 = H (76%) h) R = Me, R_1 = H, R_2 = Me (70%)



50 **51**

(15)

2. Intramolecular Pummerer Reactions

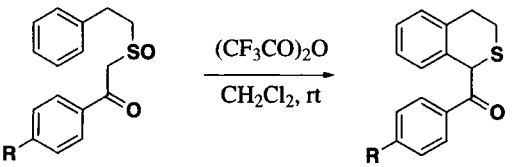
Tamura *et al.* reported that the β-ketosulfoxides **52a-b** could be converted to isothiochromans **16a** and **54b** in good yields in benzene at reflux in the presence of *p*-toluenesulfonic acid. Under these conditions, protonation of β-ketosulfoxides **52a-b** followed by dehydration presumably led to α-thiocarbocation intermediates **53a-b**.[23] The intramolecular nucleophilic attack of the aromatic rings on the these carbocation intermediates afforded 1-carbonyl substituted isothiochromans **16a** and **54b** (Eq. 16).

52a-b **53a-b** **16a; 54b**

(16)

a) R = OEt (78%) b) R =Ph (86%)

The same strategy using the intramolecular Pummerer reaction was also employed in the preparation of 1-substituted isothiochromans **56a** and **54b**.[24,25] Instead of *p*-toluenesulfonic acid, trifluoroacetic anhydride was used to initiate the cyclization process (Eq. 17). The use of the

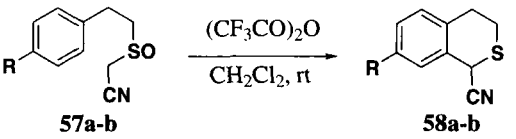


55a-b **56a, 54b**

(17)

a) R = OMe (47%) b) R = H (82%)

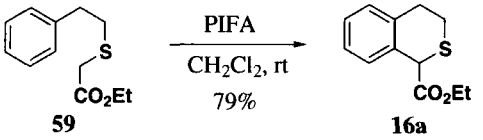
Pummerer reaction to prepare isothiochromans has been also extended to α-cyanosulfoxide substrates. Sulfoxides **57a-b**, for example, can be converted to 1-cyanoisothiochroman **58a-b** in good yields in the presence of trifluoroacetic anhydride (Eq. 18).[26]



(18)

a) R = H (71%) b) R = Me (92%)

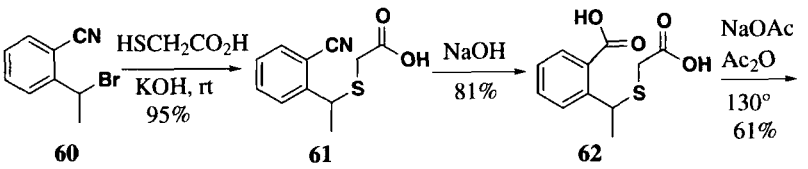
Tamura *et al.* reported that treatment of ethyl α-(1-phenethylthio)acetate (**59**) with phenyliodosyl *bis*(trifluoroacetate) (PIFA) acting as both oxidant and Lewis acid led to the formation of 1-substituted isothiochroman **16a**, a product similar to that obtained from the Pummerer cyclization of the corresponding β-ketosulfoxide **52a**.[27]



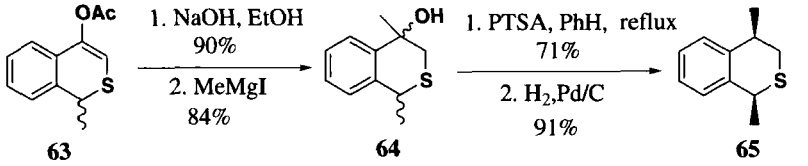
(19)

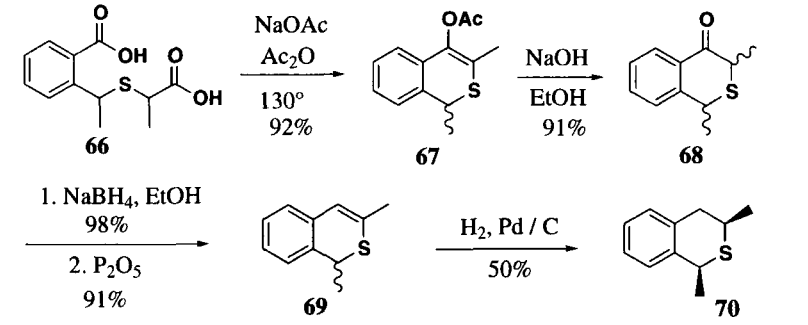
3. Dieckmann Condensation

In order to study the conformational changes of substituted isothiochromans, Whiting *et al.* developed a practical synthesis of *cis*-1,4-dimethylisothiochroman **65**.[28] The key step of this approach was based on the base-promoted Dieckmann condensation of diacid **62** at elevated temperature. Subsequent decarboxylation of the cyclized product followed by *in-situ* acylation gave 4-hydroxyisothiochroman **63** in moderate yield. This product was then converted to the desired racemic **65** (Eq. 20). By a similar approach, diacid **66** was converted to racemic *cis*-1,3-dimethylisothiochroman **70** (Eq. 21).[28]



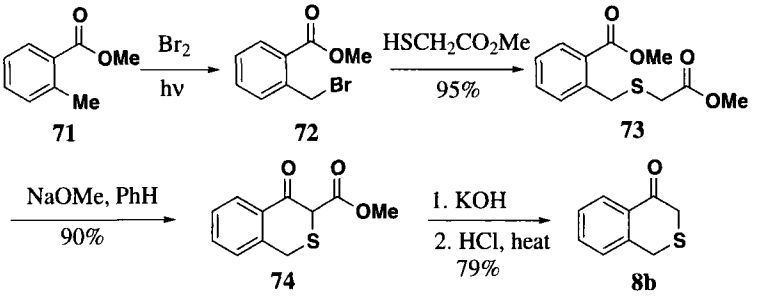
(20)





(21)

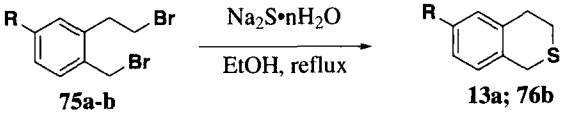
Scrowston *et al.* reported the synthesis of isothiochroman-4-one **8b** using a similar Dieckmann condensation reaction. The diester **73** cyclized under basic conditions to give β-ketoester **74**, which was decarboxylated at elevated temperature in the presence of acid after base hydrolysis to give **8b** in good overall yield (Eq. 22).[29]



(22)

4. Double Alkylation

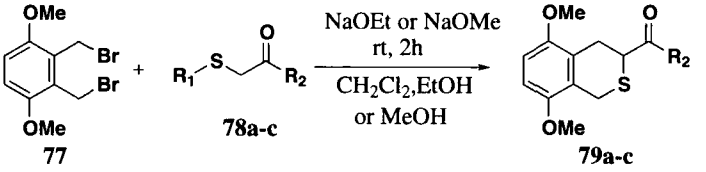
It was first reported by Braun and Zobel that 2-(2-bromoethyl)benzyl bromide **75a** reacted with sodium sulfide to give isothiochroman **13a**, which was characterized as the crystalline methiodide salt.[30] This reaction was later studied by Holliman *et al.* in ethanol at reflux; the same reaction afforded isothiochroman **13a** in 56% yield.[31] The product was formed by two consecutive S-alkylations. 6-Fluoroisothiochroman **76b** was prepared in the same manner in an unspecified yield (Eq. 23).[32]



(23)

a) R = H (56%) b) R = F (unspecified yield)

Recently, Xu and co-workers developed a new method to prepare 3-carbonyl substituted isothiochromans using a one-pot double alkylation process. Treatment of dibromide **77** with α-thiocarbonyl compounds **78a-c** in the presence of sodium alkoxides gave moderate yields of isothiochroman derivatives **79a-c** (Eq. 24).[33] The product was formed *via* initial intermolecular S-alkylation to a thiobenzylether intermediate followed by an intramolecular C-alkylation.



(24)

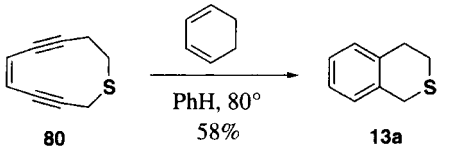
a) R_1 = H, R_2 = OMe (50%) b) R_1 = H, R_2 = OEt (46%)
c) R_1 = COPh, R_2 = Me (40%)

5. Enediyne Cyclization of Macrocyclic Sulfides

To understand the mechanism of action of antitumor agents containing an enediyne moiety in the structures such as neocarzinostatin,[34] calicheamicin,[35] esperamicins,[36] and dynemicin,[37] studies of the aromatization of enediyne systems have attracted considerable attention. Introduction of a

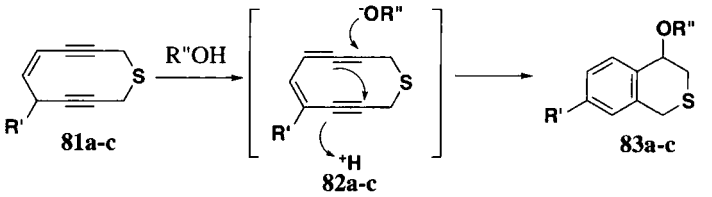
heteroatom into a macrocyclic enediyne system would lead to heterobicyclic molecule upon Bergman-Masamune cyclization.[38,39] This turns out to be a novel approach to prepare isothiochroman structures although the starting materials are usually difficult to prepare.

Sulfur-containing macrocyclic enediyne **80**, for example, undergoes a Bergman-Masamune cyclization at reflux in benzene in the presence of 1,3-cyclohexadiene to afford isothiochroman **13a** in moderate yield (Eq. 25).[40]



80 13a (25)

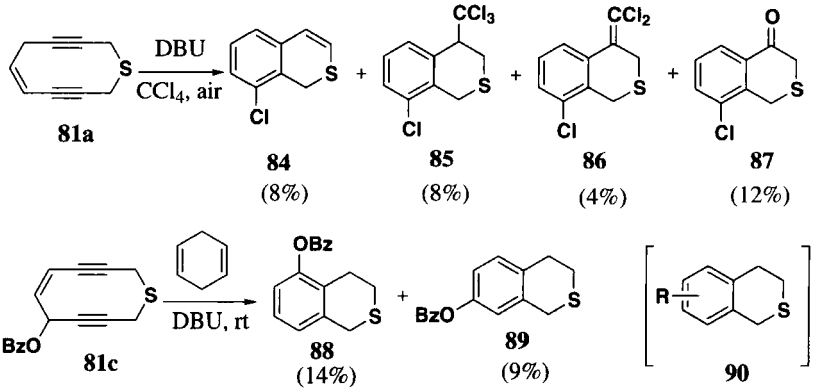
When macrocycle **81a-b** are treated with alcoholic KOH in DMSO, 4-alkoxyisothiochroman **83a-b** are obtained.[41] In the absence of alcohol, the reaction of **81c** in DMSO and Tris-HCl buffer solution (pH = 8.5) gives the hydroxyl analog **83c**.[42] The formation of **83a-c** was proposed to occur through an allene intermediate **82** by a polar anionic pathway (Eq. 26).



81a-c 82a-c 83a-c (26)

a) R' = H, R" = Me (58%) KOH, DMSO, MeOH;
b) R' = H, R" = Et (43%) KOH, DMSO, EtOH;
c) R' = OCOPh, R" = H (10%) DMSO, Tris-HCl buffer (pH = 8.5).

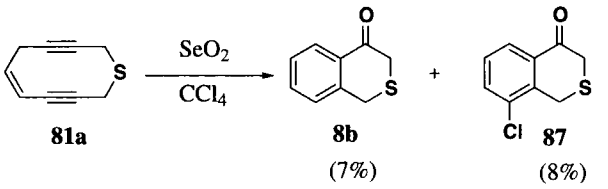
Treatment of the same macrocycle **81a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in carbon tetrachloride in the presence of oxygen (air) afforded a variety of 8-chloroisothiochroman derivatives (**84-87**).[41] The transannular cyclization of the substituted macrocycle **81c** in the presence of 1,4-cyclohexadiene gives isothiochromans **88** and **89** in low yields (Eq. 27).[42] Free radical intermediates such as **90** are proposed to account for the formation of the products.



81a 84 (8%) 85 (8%) 86 (4%) 87 (12%)

81c 88 (14%) 89 (9%) 90 (27)

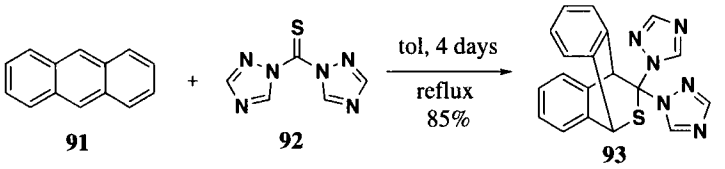
The reaction of **81a** with SeO_2 in carbon tetrachloride gives isothiochroman-4-ones **8b** and **87** in low yields (Eq. 28).[43]



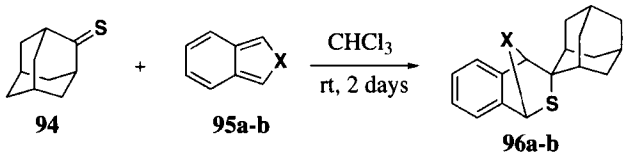
81a **8b** (7%) **87** (8%) (28)

6. Diels-Alder Reactions

The Diels-Alder reaction with either the diene or the dienophile containing a heteroatom has been often used in preparing heterocyclic compounds. Dienes and dienophiles containing oxygen as the heteroatom such as ketones and aldehydes are widely available. On other hand, the corresponding sulfur compounds are scarce due to the instability of thioketones and thioaldehydes. The paucity of thioketones and thioaldehydes, however, is compensated by their superior reactivity in the cycloaddition reactions compared to that of the oxygen analogs. With these stable thiocarbonyl compounds, this approach provides easy access to isothiochroman systems. Thus, treatment of anthracene **91** with 1,1'-thiocarbonyl*bis*(1,2,4-triazole) **92** in toluene at reflux gives isothiochroman cycloadduct **93** (Eq. 29).[44] Similarly, Diels-Alder reactions of adamantanethione **94** with isoindole **95a** and isobenzofuran **95b** in chloroform at room temperature afford cycloadduct **96a** and **96b** in 96% and 79% yields, respectively (Eq. 30).[45]



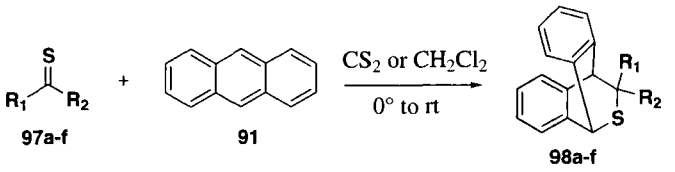
91 **92** **93** (29)



94 **95a-b** **96a-b** (30)

a) X = $NCO_2(t\text{-Bu})$ (96%) b) X = O (79%)

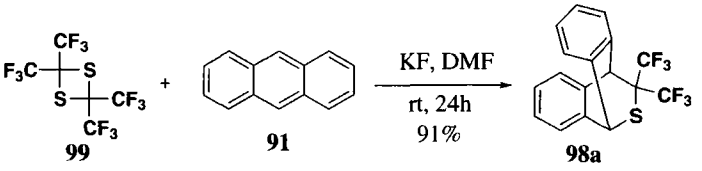
Perfluorothioketones have been found to be the most reactive dienophiles among the thiocarbonyl compounds. For example, the [4+2] cycloaddition of hexafluorothioacetone **97a** with anthracene **91** is complete within minute at 0° in carbon disulfide to give a quantitative yield of the ring fused isothiochroman structure **98a**.[46] The Diels-Alder reactions of perfluorothioketone **97b**[46] as well as perhalogenalkyl thioacetyl fluorides **97c-f**[46,47] with anthracene **91** are illustrated in Eq. 31. The



(31)

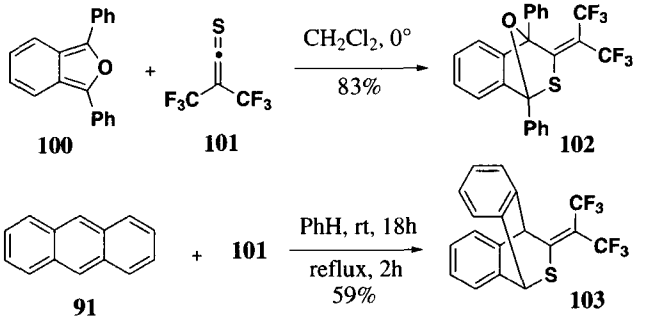
a) R_1, $R_2 = CF_3$ (100%) b) $R_1 = CF_2CF_3$, $R_2 = CF_3$ (95%) c) $R_1 = CF_3$, $R_2 = F$ (93%)
d) $R_1 = CF_2CF_3$, $R_2 = F$ (61%) e) $R_1 = CF_2Cl$, $R_2 = F$ (71%) f) $R_1 = CF_2Br$, $R_2 = F$ (76%)

dimer of hexafluorothioacetone (**99**), can also undergo a [4+2] cycloaddition reaction with anthracene to form product **98a** in good yield (Eq. 32).[48]



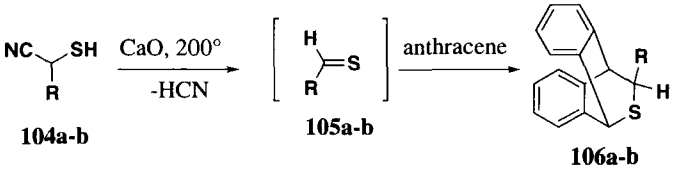
(32)

Thioketene can also serve as a dienophile. The reaction of 1,3-diphenylisobenzofuran **100** with *bis*(trifluoromethyl)thioketene **101**, for example, gives Diels-Alder adduct **102** (Eq. 33).[49] Similarly, the treatment of anthracene **91** with the same thioketene yields 12-(hexafluoroisopropylidene)-11-thia-9,10-dihydro-9,10-ethanoanthracene **103** (Eq. 33).[49]



(33)

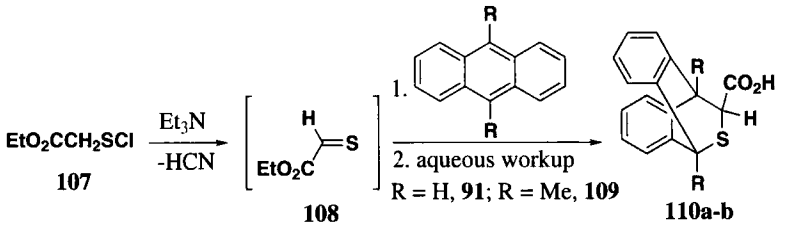
Most thioaldehydes are too reactive to be isolated. They can be, however, chemically characterized by their cycloaddition with dienes. For example, thiocyanohydrins **104a-b** have been used to generate methanethial **105a** and ethanethial **105b** respectively under vacuum gas-phase dehydrocyanation conditions. In the presence of anthracene, both **105a** and **105b** undergo a [4+2] cycloaddition reaction to afford Diels-Alder adducts **106a-b** (Eq. 34).[50]



(34)

a) R = H (unspecified yield) b) R = Me (unspecified yield)

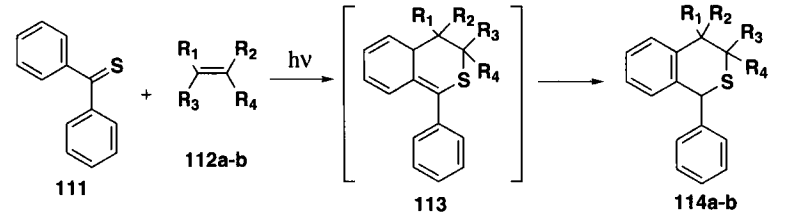
Similar treatment of sulfenyl chloride **107** with triethylamine in benzene generates labile thioaldehyde **108**, which can be trapped *in situ* with anthracenes **91** and **109** to give cycloadducts **110a-b** in good yields (Eq. 35).[51]



(35)

a) R = H (76%) b) R = Me (61%)

Thiobenzophenone can be used as the diene system in the [4+2] cycloaddition reaction. Irradiation of a solution of thiobenzophenone (**111**) in tetramethylethylene **112a** at -78° gives a highly substituted isothiochroman **114a**.[52] The reaction of thiobenzophenone with acrylonitrile (**102b**) under similar conditions furnishes isothiochroman **114b**.[52] A bicyclotriene intermediate **113**, derived from the photocycloaddition of thiobenzophenone to the olefin, has been proposed to account for this transformation (Eq. 36).

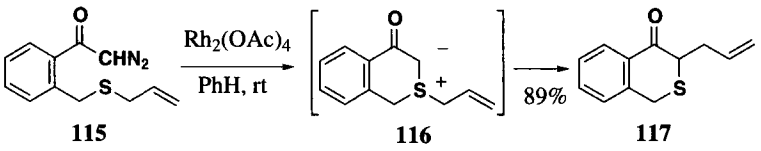


(36)

a) R_1, R_2, R_3, R_4 = Me (35%) b) R_1 = CN, R_2, R_3, R_4 = H (35%)

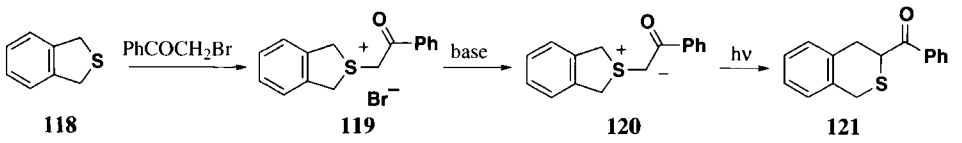
7. Sulfonium Ylides Rearrangement

Treatment of α-diazoacetophenone **115** with rhodium(II) acetate in benzene gives rise to isothiochroman-4-one **117** in good yield.[53] The formation of **117** is consistent with the generation of an initial carbenoid, followed by capture by the neighboring sulfur to generate sulfonium ylide intermediate **116**, which then undergoes a subsequent 2,3-sigmatropic rearrangement (Eq. 37).



(37)

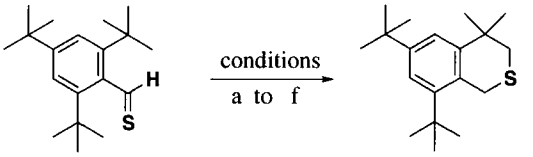
Alkylation of 1,3-dihydrobenzo[*c*]thiophene **118** with 2-bromoacetophenone generates phenacylsulfonium salt **119**. Treatment of the salt with base affords 3,4-benzotetramethylenesulfonium phenacylide **120**. Under irradiation conditions, the sulfonium ylide **120** undergoes Stevens rearrangement to generate 3-benzoylisothiochroman **121** in unspecified yield (Eq. 38).[54]



118 119 120 121 (38)

8. Miscellaneous Reactions

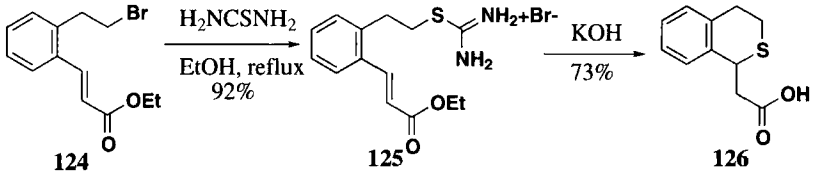
Okazaki *et al.* has reported that the reaction of thiobenzaldehyde **122** with 2,4,6-tri-*t*-butylphenylmagnesium bromide in THF at reflux afforded 6,8-di-*t*-butyl-4,4-dimethylisothiochroman **123** in 80% yield (Eq. 39). The formation of the product was proposed to occur *via* the anionic radical of the thioaldehyde.[55] A variety of other conditions (Eq. 39) also promoted the formation of isothiochroman **123**.[56-61] Under both thermal and radical conditions, product **123** was obtained in good yields. Under photolytic conditions, the reaction gave a very good yield of the product in benzene but low yield in alkaline media.



122 **123** (39)

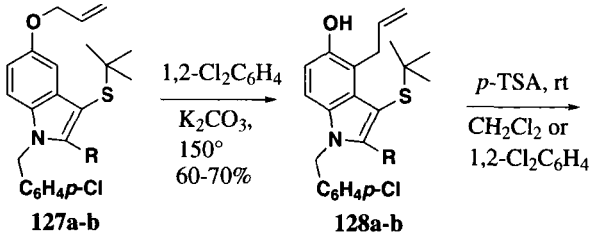
a) (80%) 2,4,6-tri-*t*-BuPhMgBr, THF, reflux
b) (93%) CH_2N_2, THF, reflux
c) (97%) 200°, PhH, sealed tube
d) (81%) AIBN, PhH, 80°
e) (55%) Ph_2CN_2, THF, reflux
f) (91-96%) hv, PhH

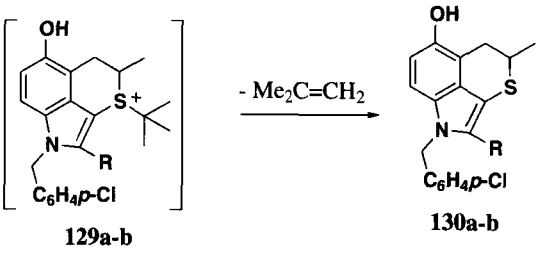
Bunce and co-workers reported a tandem S_N2 alkylation/Michael addition sequence for the preparation of 1-substituted isothiochroman. Alkylation of phenylethyl bromide **124** with thiourea afforded salt **125**, which was not isolated; the reaction mixture was treated with KOH to liberate the thiol which underwent intramolecular Michael addition with the α,β-unsaturated ester to give isothiochroman **126** (Eq. 40).[62]



124 **125** **126** (40)

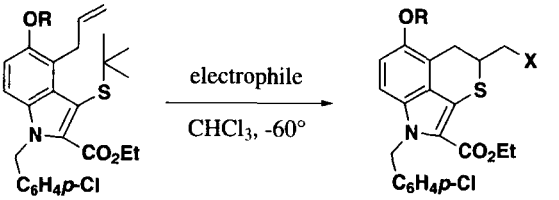
In refluxing dichlorobenzene, the allyl ether functionality of the substituted indole **127a-b** undergoes regioselective Claisen rearrangement to give C-4 allyl substituted indoles **128a-b**. The allyl group subsequently undergoes cyclization with the neighboring C-2 *t*-BuS substituent to form tricyclic thiopyranoindoles **130a-b** in good yields under acidic conditions. The reaction was proposed to occur through the attack of the protonated double bond by the sulfur atom in **128a-b** to form a sulfonium ion intermediate **129a-b**. Elimination of isobutylene from **129a-b** gives the products **130a-b** (Eq. 41).[63]





(41)

Besides acids, electrophiles such as Br_2, I_2, and $Hg(OAc)_2$ can also induce the cyclization of allylindole **128b-c** to generate functionalized thiopyranoindoles **131c-e** (Eq. 42).[64]



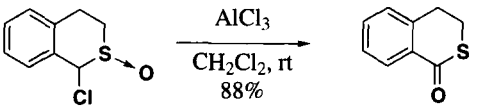
(42)

128b-c b) R = H. c) R = Me

131c-e

c) R = H, X = Br (82%)
d) R = H, X = I (87%)
e) R = Me, X = HgCl (80%)

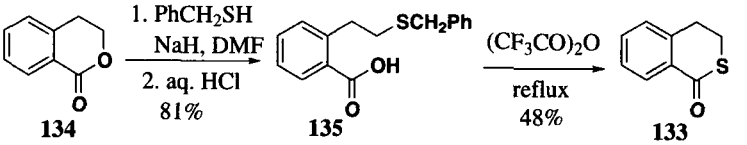
Isothiochroman-1-one **133** can be prepared from 1-chloroisothiochroman-2-oxide **132** in good yield (Eq. 43).[65]



(43)

132 **133**

Another interesting way to prepare isothiochroman-1-one **133** was reported by Lumma, Jr. *et al.* starting from isochroman-1-one **134** in a two-step process (Eq. 44).[66]

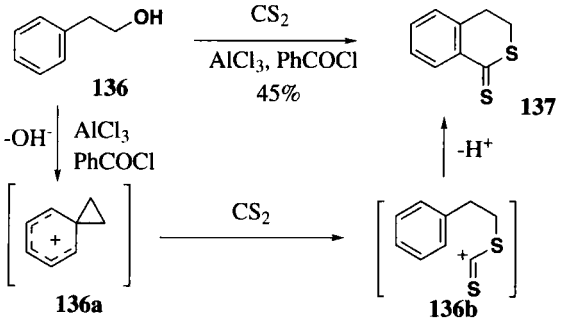


(44)

134 **135** **133**

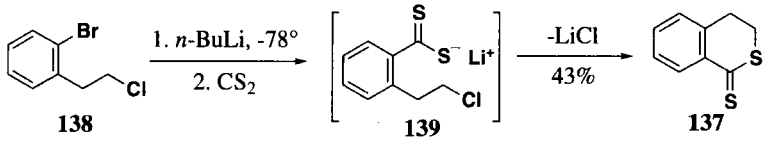
The reaction of phenethyl alcohol (**136**) and carbon disulfide in the presence of $AlCl_3$ and benzoyl chloride provides a direct method to prepare isothiochroman-1-thione **137**.[67] A plausible

mechanism that was proposed for this reaction involves initial generation of stabilized phenonium ion **136a** followed by electrophilic reaction with carbon disulfide, and finally ring closure of **136b** through an intramolecular Friedel-Crafts reaction (Eq. 45).



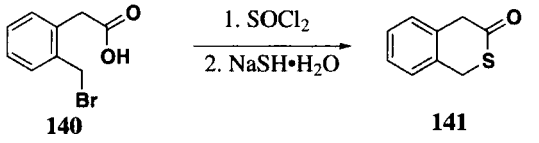
(45)

Voβ *et al.* reported an additional method to prepare isothiochroman-4-thione **137**.[68] Treatment of α-bromophenethyl chloride **138** with *n*-butyllithium followed by addition of carbon disulfide generated anionic intermediate **139**, that underwent intramolecular alkylation to form the product **137** (Eq. 46).



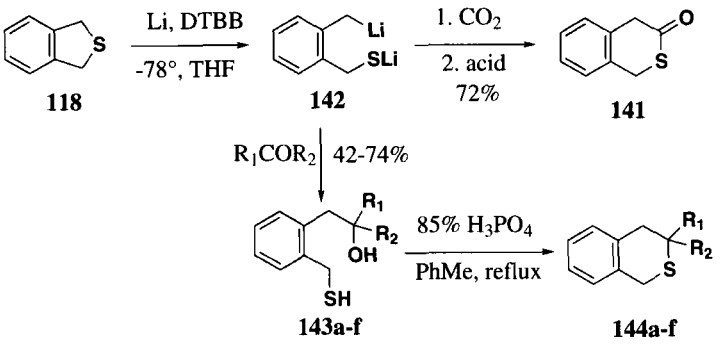
(46)

The reaction of *o*-(bromomethyl)phenylacetic acid **140** with $SOCl_2$ provides the corresponding acid chloride, followed by treatment with sodium hydrosulfide hydrate afforded isothiochroman-3-one **141** in unspecified yield in a one-pot reaction (Eq. 47).[69].



(47)

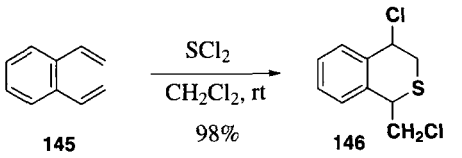
Recently, a new method for the synthesis of 3-substituted isothiochroman was reported by Yus and co-workers.[70] The reaction of 1,3-dihydrobenzo[*c*]thiophene **118** with an excess of lithium metal and a catalytic amount of 4,4'-di-(*t*-butyl)biphenyl (DTBB) in THF at -78° generated a dianion intermediate **142**. Trapping the dianion with carbon dioxide followed by acid workup directly gave isothiochroman-3-one **141** in 72% yield. The dianion could also react with ketones and aldehydes to give functionalized thiols **143a-f**. Treatment of these thiols with phosphoric acid in refluxing toluene gave rise to isothiochromans **144a-f** in good overall yields (Eq. 48).



(48)

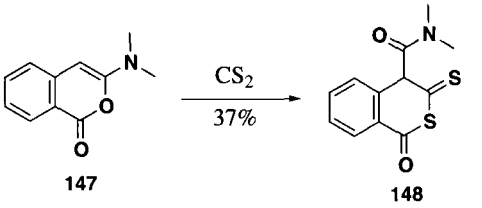
a) R_1= H, R_2 = *i*-Pr (51%) b) R_1 = H, R_2 = t-Bu (35%) c) R_1= H, R_2 = Ph (97%)
d) R_1 = R_2 = Me (89%) e) R_1, R_2 = -$(CH_2)_4$- (85%) f) R_1 = Me, R_2 = Ph (94%)

Under high dilution conditions, simultaneous addition of sulfur dichloride and *o*-divinylbenzene **145** results in the formation of a mixture of *cis*- and *trans*-isomers of 1-chloromethyl-4-chloroisothiochroman **146** in good yield (Eq. 49).[71]



(49)

The reaction of 1*H*-2-benzopyran-1-one **147** with carbon disulfide generates 1-oxo-isothiochroman-3-thione derivative **148** (Eq. 50).[72,73] An *ene* reaction mechanism has been proposed for this transformation.



(50)

II. REACTIONS OF ISOTHIOCHROMANS

The reactions of isothiochromans discussed in this section are basically restricted to the saturated, heterocyclic ring. Very little information has been reported concerning reactions taking place on the aromatic ring, which are not included here.

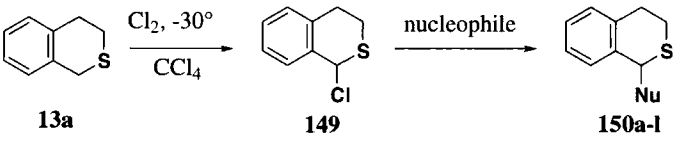
1. Reactions at the C-1 Position of Isothiochromans

Being both benzylic and α– to the sulfur atom, the C-1 position of isothiochroman structure is the principal site of reactivity.

a. Cationic Reactions

Böhme and co-workers reported that the reaction of isothiochroman **13a** with chlorine at -30° in carbon tetrachloride gave 1-chloroisothiochroman **149**,[65,66] which serves as a good substrate for a

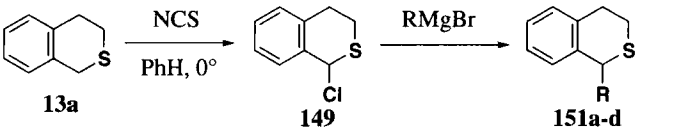
number of nucleophilic substitutions such as reaction with Grignard reagents, thiols, amines, and alcohols to provide functionalized isothiochromans **150a-l** in yields ranging from 8-62% (Eq. 51).[74-76]



13a **149** **150a-l** (51)

a) MeI, Mg, Et_2O; Nu = Me (56%) b) PhMgBr, Et_2O; Nu = Ph (38%)
c) EtSH, Na, CCl4; Nu = SEt (38%) d) Et_2NH, PhH; Nu = NEt_2 (8%)
e) EtOH, Py, CCl4; Nu = OEt (62%) f) NaN_3, DMF; Nu = N_3 (62%)
g) $NH_2CSNHEt$; Nu = NHCSNHEt (47%) h) NH_2COH; Nu = NHCOH (80%)
I) NH_2CO_2Me; Nu = $NHCO_2Me$ (94%) j) succinimide; Nu = succinimide (61%)
k) NH_2CONH_2; Nu = $NHCONH_2$ (67%) l) AgNCO; Nu = NCO (31%)

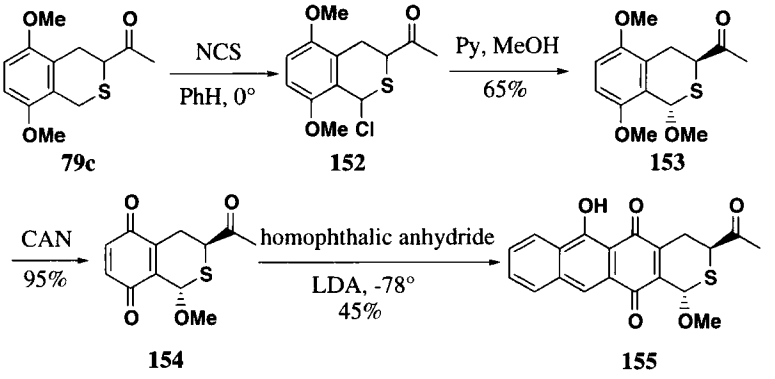
Alternatively, 1-chloroisothiochroman **149** was generated by treatment of isothiochroman **13a** with *N*-chlorosuccinimide (NCS) in benzene at 0°.[16] The chlorination took place exclusively at the C-1 position of isothiochroman. 1-Chloroisothiochroman **149** was then alkylated with alkynyl and vinyl Grignard reagents to yield the C-1 substituted isothiochromans **151a-d** (Eq. 52).[77,78]



13a **149** **151a-d** (52)

a) R = C≡C-Me (53%) b) R = C≡C-Bu (72%)
c) R = C≡C-Ph (89%) d) R = $CH{=}CH_2$ (65%)

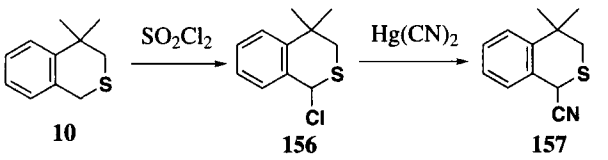
The reaction of substituted isothiochroman **79c** with NCS gave 1-chloroisothiochroman **152**, which without isolation, was converted to 1-methoxy-1,3-*trans*-isothiochroman analog **153** with methanol and pyridine. Oxidative demethylation of **153** with ceric ammonium nitrate in the presence of $NaHCO^3$ gave rise to thiopyranquinone **154**. Treatment of **154** with the lithium enolate of homophthalic anhydride gave heterocyclic anthracyclinone analog **155** in 45% yield (Eq. 53).[33,79,80]



79c **152** **153** (53)

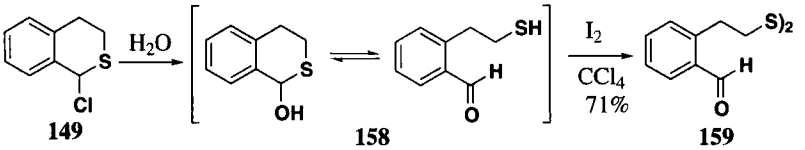
154 **155**

Alternatively, 1-chloroisothiochromans can be efficiently prepared by the reaction of isothiochroman with sulfuryl chloride. For example, treatment of isothiochroman **13a** with one equivalent of sulfuryl chloride in refluxing carbon tetrachloride gives **149** in quantitative yield.[81] 1-Cyanoisothiochroman **157** has been prepared using the chloroisothiochroman **156** which is derived similarly from the reaction of 4,4-dimethylisothiochroman **10** with sulfuryl chloride (Eq. 54).[82,83]



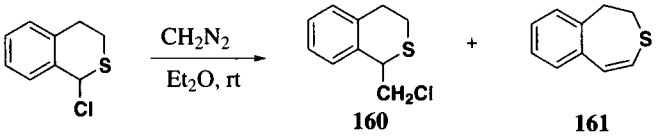
10 **156** **157** (54)

The substitution reaction of 1-chloroisothiochroman **149** with water as a nucleophile gives an unstable 1-hydroxyisothiochroman **158**, which dimerizes upon oxidation with iodine to form **159** (Eq. 55).[65]



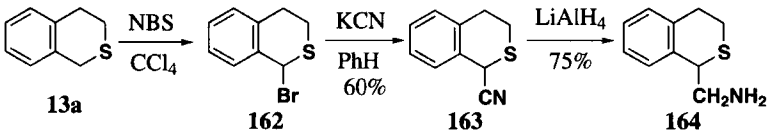
149 **158** **159** (55)

Reaction of 1-chloroisothiochroman **149** with diazomethane gives rise to a mixture comprised of 1-chloromethylisothiochroman **160** and ring expanded product **161** in about 1:1 ratio (Eq. 56).[84]



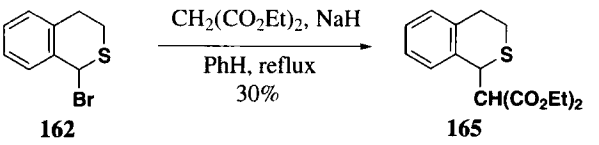
149 **160** 26% **161** 27% (56)

Pellicciari *et al.* reported a synthesis of 1-aminomethyl isothiochroman **164**, a structurally rigid phenylethylamine analog. Bromination of a simple isothiochroman **13a** with NBS in carbon tetrachloride affords unstable 1-bromoisothiochroman **162**,[85] which was alkylated with KCN in benzene to give rise to 1-cyanoisothiochroman **163** in 60% overall yield. The target molecule **164** was readily obtained by reduction of the cyano group using $LiAlH_4$ (Eq. 57).[3a]



13a **162** **163** **164** (57)

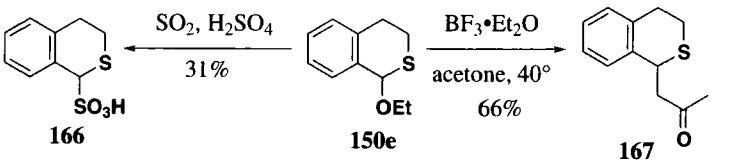
Alkylation of 1-bromoisothiochroman **162**, which can also be obtained from the reaction of **13a** and bromine,[86] with the enolate of diethyl malonate gives 1-substituted isothiochroman **165** (Eq. 58).[87]



(58)

162 **165**

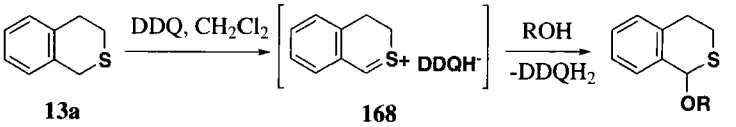
Upon treatment with acids, 1-ethoxyisothiochroman **150e** is converted to the C-1 cationic intermediate, which can then be trapped by nucleophiles including SO_2[74] and acetone (Eq. 59).[88]



(59)

166 **150e** **167**

Xu *et al.* developed a direct method to introduce an alkoxy group into the 1-position of isothiochroman molecule. Oxidative reaction of isothiochroman **13a** with DDQ generated a cationic intermediate **168**, stabilized by $DDQH^-$. Coupling reactions of the intermediate with alcohols afforded 1-alkoxyisothiochromans **169** and **150e** in good yields (Eq. 60).[89]

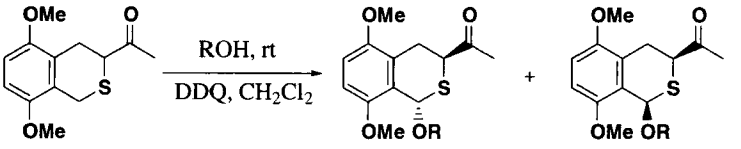


(60)

13a **168**

169; R = Me (89%)
150e; R = Et (91%)

With 3-substituted isothiochroman such as **79c**, the oxidative coupling reactions with alcohols gave a mixture of *cis* and *trans* 1,3-disubstituted isothiochromans **170a-d** and **171a-d** in good yields (Eq. 61).[90] The stereoselectivity in favor of the *trans* isomer was rationalized in terms of steric interaction of the attacking nucleophiles with the C-3 acetyl substituent.



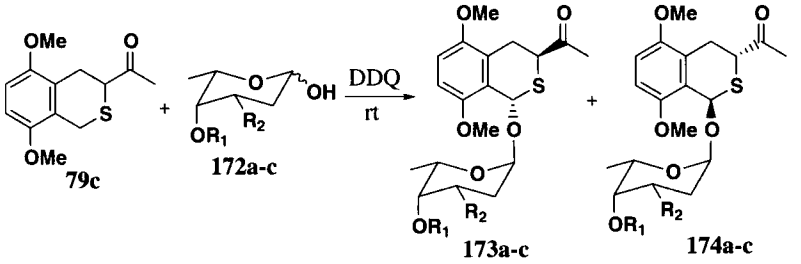
(61)

79c **170a-d** **171a-d**

a) R = Me; 170/171 = 3:1 (86%) b) R = *i*-Pr; 170/171 = 4:1 (83%)
c) R = *t*-Bu; 170/171 = 2:1 (52%) d) R= $(CH_2)_2NHBoc$; 170/171 = 3:1 (91%)

The DDQ-induced oxidative coupling reactions with alcohols were extended to carbohydrate chemistry. The oxidative glycosidations of isothiochroman **79c** with the sugars **172a-c** using DDQ gave rise to the benzylic glycosides **173a-c** and **174a-c** in good yields (Eq. 62).[91] The reaction was found to be stereoselective since only 1,3-*trans* glycosides were isolated and no 1,3-*cis* glycosides were observed. This was ascribed to the steric bulkiness of the sugar, leading to preferential

attack of the benzylic cation *trans* to the 3-acetyl group. Another interesting feature of this glycosidation is the high anomeric selectivity. Although a mixture of α– and β- anomeric free sugars **172a-c** was used, only α-glycosides were isolated from the reaction. This was explained by the thermodynamic equilibrium of the both α- and β-glycosides, in which the α-forms were favored thermodynamically due to the anomeric effects.

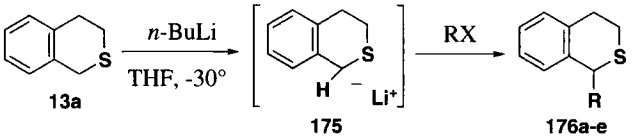


(62)

a) R_1 = Ac, R_2 = OAc α/β = 1:1 **173/174** = 3:2 (79%)
b) R_1 , R_2 = -C(Me)$_2$O- α/β = 5:1 **173/174** = 2:1 (63%)
c) R_1 = PNB, R_2 = NHCOCF$_3$ α/β = 1:1 **173/174** = 1:1 (47%)

b. Carbanionic Reactions

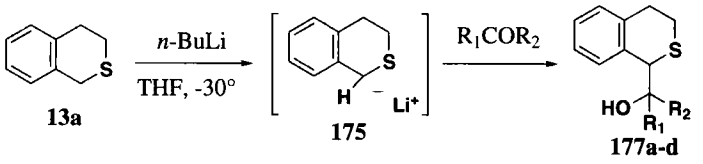
Böhme *et al.* found that treatment of simple isothiochroman **13a** with *n*-butyllithium in THF at -30° could generate lithium carbanion intermediate **175**.[92] Similar to other carbanion chemistry, **175** is highly reactive intermediate and can undergo nucleophilic substitution reaction with a variety of alkylhalides. This process provides a facile method to access C-1 functionalized isothiochromans from unsubstituted isothiochroman derivatives. For example, the reaction of **13a** with *n*-butyllithium in THF followed by addition of isopropyl iodide gave 1-isopropylisothiochroman **176b** in 91% yield (Eq. 63).[92]



(63)

a) R = Me, X = I (90%) b) R = *i*-Pr, X = I (91%) c) R = $(CH_2)_2CH(OEt)_2$ (85%)
d) R = TMS, X = Cl; (90%) e) R = CH_2Ph, X = Cl (90%)

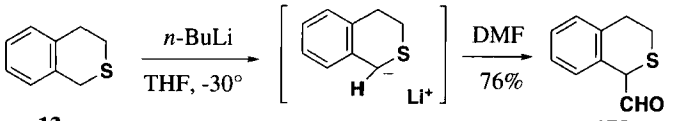
The same research group also studied the aldol condensation of the **175** with aldehydes and ketones to produce **177a-d**.[92] When asymmetric carbonyl compounds were used, a mixture of two diastereoisomers of the products was obtained in roughly about 1:1 ratio of the *threo*- and *erythro*-forms, which could be readily separated by flash column chromatography.



(64)

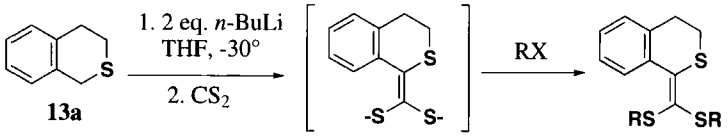
a) R_1 = H, R_2 = Ph (72%) b) R_1 = H, R_2 = Ph(*p*-OMe) (65%)
c) R_1 = R_2 = Ph (89%) d) R_1, R_2 = -$(CH_2)_4$- (46%)

Reaction of the carbanion **175** with *N,N*-dimethylformamide (DMF) affords isothiochroman-1-yl aldehyde **178** (Eq. 65).[93]



13a **175** **178** (65)

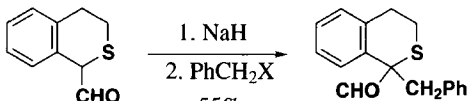
Treatment of isothiochroman **13a** with two equivalents of *n*-butyllithium in THF at -30°, followed by reaction with carbon disulfide, results in the formation of dianion intermediate **179**. Subsequent nucleophilic substitution with alkyl halides affords ketene mercaptals **180a-c** in good yields (Eq. 66).[92]



13a **179** **180a-c** (66)

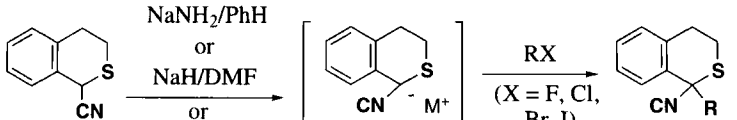
a) R = Me, X = I (85%) b) R = Et, X = I (70%) c) RX = $Br(CH_2)_3Br$ (60%)

With an electron-withdrawing group already substituted at the C-1 position, the C-1 carbanion intermediate of isothiochroman can be generated by a base other than *n*-butyllithium, which required for unsubstituted isothiochroman systems. For example, the C-1 carbanion of 1-isothiochromanaldehyde **178** can be generated by use of NaH as a base. The nucleophilic substitution reaction of the anion with benzyl halide affords 1,1-disubstituted isothiochroman derivative **181** (Eq. 67).[93]



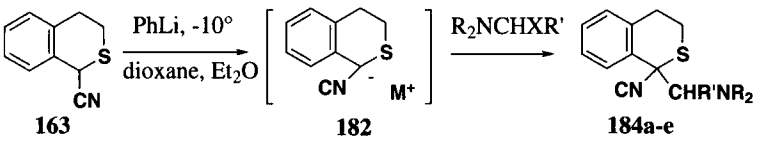
178 **181** (67)

The carbanion of 1-cyanoisothiochroman **163** can be generated by a number of bases including $NaNH_2$ in benzene,[94] NaH in DMF,[95] and organolithium reagents.[96,97] Subsequent nucleophilic substitution of **182** with a variety of electrophiles gives 1,1-disubstituted isothiochroman derivatives **183a-k** in yields ranging from 30 to 98% (Eq. 68).[94,95] Carbanion **182** can also react with α-haloamines to give 1-cyano-1-aminomethyl isothiochroman derivatives **184a-e** (Eq. 69).[96] Anion **163**



163 **182** **183a-k** (68)

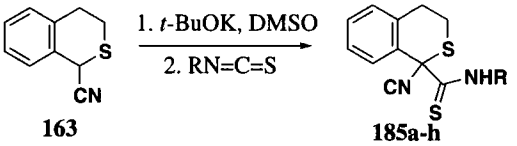
a) R = Me (90%) b) R = CH_2OMe (85%) c) R = CH_2SMe (80%)
d) R = $(CH_2)_2Ph$ (90%) e) R = COPh (98%) f) R = CO_2Me (37%)
g) R = $CONEt_2$ (60%) h) R = CH_2CCH (78%) i) R = D, X = OD (91%)
j) R = CH_2CO_2Et (30%) k) R = Ph[2,4-$(NO_2)_2$] (37%)



163 182 184a-e (69)

a) R' = H, NR_2 = NMe_2 (43%) b) R' = H; NR_2 = NEt_2 (47%)
c) R' = H, NR_2 = pyrrolidine (33%) f) R' = H; NR_2 = morpholine (55%)
d) R' = Ph; NR_2 = morpholine (45%)

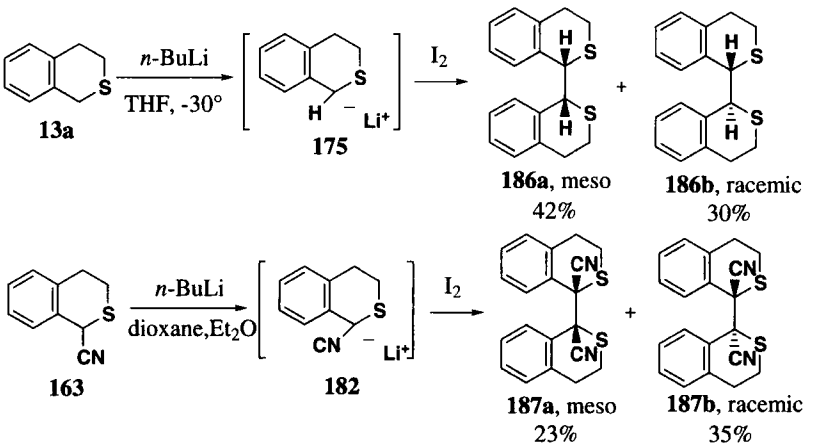
can also be prepared by using potassium *t*-butoxide; its reaction with alkyl isothiocyanates in DMSO affords 1-cyanoisothiochoman-1-thiocarbamide derivatives **185a-h** in moderate yields (Eq. 70).[98]



163 185a-h (70)

a) R = Me (10%) b) R = Et (61%) c) R = *n*-Pr (62%)
d) R = *n*-Bu (76%) e) R = $CH_2CH{=}CH_2$ (27%) f) R = c-C_6H_{11} (62%)
g) R = Ph (40%) h) R = CH_2Ph (88%)

Treatment of the carbanion **175** with iodine results in the formation of dimeric structures **186a** and **186b** in about 4:3 ratio.[92] The major oxidation product **186a** exists in *meso*-form and the minor as *racemic* form. Similarly, the iodine oxidation of 1-cyanoisothiochroman carbanion **182** gave rise to dimers **187a** and **187b** in a slightly different ratio (3:4) of *meso*- and *racemic* diastereoisomers (Eq. 71).[97]

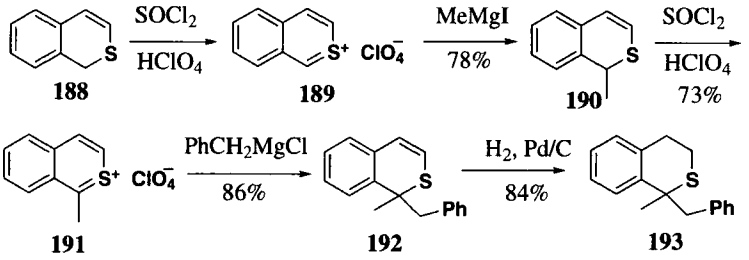


(71)

c. Reactions of Sulfonium Ylides, Sulfonium Salts and Sulfones of Isothiochromans

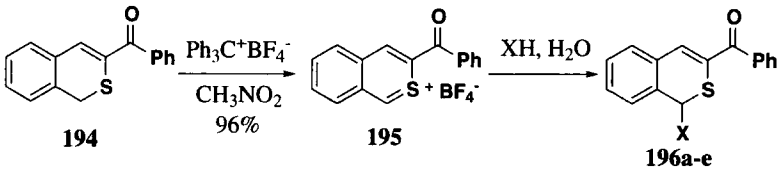
Complementary to other direct methods, the following reaction sequence provides an alternative approach to functionalize the C-1 position of isothiochroman. This usually consists of three steps: (a) converting isothiochroman to its ylide, salt, sulfoxide or sulfone that allows the activation of the C-1 position; (b) introducing a functional group at the C-1 position; (c) converting the ylide, salt,

sulfoxide or sulfone back to the isothiochroman. The preparation of 1,1-disubstituted isothiochroman **193** shown in the following scheme is a good example demonstrating the utility of such a strategy. 2-Thianaphthylium perchlorate **189**, obtained from the reaction of isothiochromen **188** with $SOCl_2$ and perchloric acid, is converted into 1-methylisothiochromen **190** by addition of methylmagnesium iodide. The perchlorate salt **191** generated in a fashion similar to **189** underwent a second addition with benzylmagnesium chloride to afford 1-benzyl-1-methylisothiochromen **192**, which is reduced by H_2 using Pd/C as a catalyst to saturated isothiochroman derivative **193** in good overall yield (Eq. 72).[99]



(72)

Benzothiopyrylium salt **195** can be generated from isothiochromen **194** and triphenylcarbenium tetrafluoroborate in nitromethane. The subsequent reactions of the sulfonium salt with activated methylene compounds afford C-1 functionalized isothiochromens **196a-e** in yields ranging from 29-87% (Eq. 73).[100]

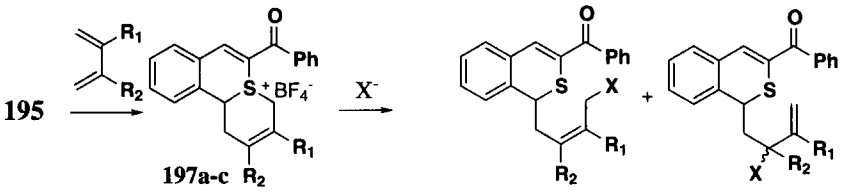


(73)

a) X = CH_2COMe (52%) b) X = $CH(CO_2Me)_2$ (29%) c) X = $CH(COMe)_2$ (73%)
d) X = $CH(COPh)_2$ (87%) e) X = $CH(COMe)CO_2Et$ (82%)

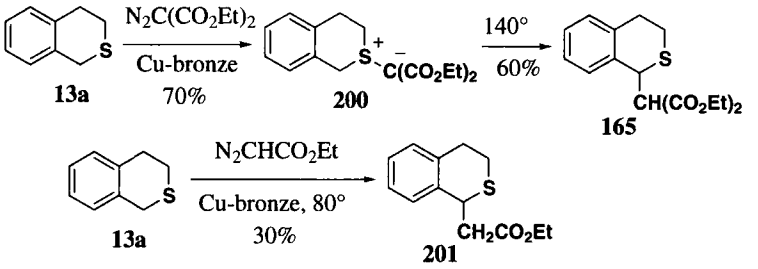
Benzothiopyrylium salt **195** can also undergo polar cycloaddition reactions with conjugated dienes to form benzo-fused bicyclic sulfonium salts **197a-c**. Reactions of these cycloadducts with a variety of nucleophiles open the newly formed ring to afford 1-allyl substituted isothiochromens **198a-h** as major products along with 1-homoallylisothiochromens **199a-h** as minor products (Eq. 74).[100]

The copper-bronze catalyzed decomposition of diethyl diazomalonate in isothiochroman **13a** leads to the formation of sulfonium ylide **200**. Upon heating, the ylide undergoes a Stevens rearrangement to produce C-1 functionalized isothiochroman derivative **165**.[101] At elevated temperature, the reaction of isothiochroman **13a** with ethyl diazoacetate in the presence of copper-bronze catalyst gives C-1 functionalized isothiochroman **201** directly (Eq. 75).[101]



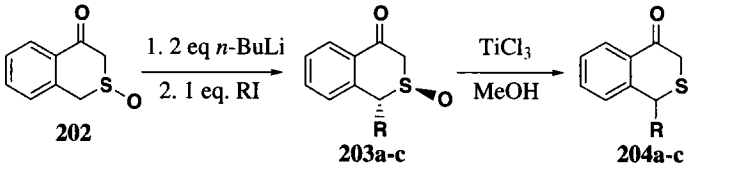
a) $R_1 = R_2 = Me$ (79%)
b) $R_1 = Me$, $R_2 = H$ (96%)
c) $R_1 = R_2 = H$ (82%)

a)	$R_1, R_2 = Me$, X = OH	(74%)	(25%)
b)	$R_1, R_2 = Me$, X = OMe	(87%)	(12%)
c)	$R_1, R_2 = Me$, X = NHPh	(85%)	(0%)
d)	$R_1, R_2 = Me$, X = SPh	(96%)	(0%)
e)	$R_1, R_2 = Me$, X = SePh	(80%)	(0%)
f)	$R_1, R_2 = Me$, X = CN	(54%)	(0%)
g)	R_1, Me, $R_2 = H$, X = OMe	(85%)	(14%)
h)	$R_1, R_2 = H$, X = OMe	(73%)	(2%)



(75)

Introduction of a functional group at the C-1 position can also be facilitated by using higher oxidation states of the sulfur atom in the isothiochroman molecule. For example, treatment of isothiochroman-4-one-2-oxide **202** with two equivalents of *n*-butyllithium, followed by addition of alkyl iodides, leads to isothiochroman-2-oxide derivatives **203a-c** in good yields. Reaction with alkyl iodides occurs only at the C-1 position, and no C-3 alkylation is observed. The reactions are also found to be stereoselective, and the C-1 alkyl groups reside *trans* to the sulfoxide group. Reductions of isothiochroman oxides **203a-c** with $TiCl_3$ in methanol afford isothiochroman analogs **204a-c** in excellent yields (Eq. 76).[102]



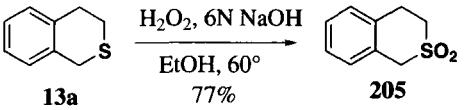
a) R = Me	(84%)	(98%)
b) R = Et	(63%)	(98%)
c) CH_2Ph	(66%)	(98%)

2. Reactions at the Sulfur Atom of Isothiochromans

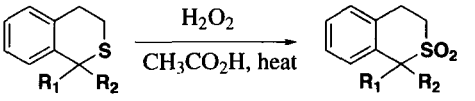
Besides reactions directly occurring at the sulfur atom, processes involving the breakage of the bonds are also included in this section.

a. Oxidation

Being dialkyl sulfides, isothiochromans are readily oxidized by a variety of reagents. For example, treatment of isothiochroman **13a** with hydrogen peroxide in basic ethanolic solution affords isothiochroman-S,S-dioxide **205** in good yield (Eq. 77).[103] Oxidation of more functionalized isothiochromans **206a-g** could be also carried out using hydrogen peroxide in acetic acid (Eq. 78).[74,94]



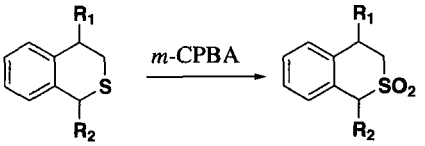
13a **205** (77)



206 **207a-g** (78)

a) R_1 = H; R_2 = Me (50%) b) R_1 = H; R_2 = Et (55%)
c) R_1 = H; R_2 = Ph (53%) d) R_1 = H; R_2 = SO_3H (62%)
e) R_1 = CN; R_2 = Me (86%)) f) R_1 = CN; R_2 = Et (58%
g) R_1 = CN; R_2 = CH_2OMe (86%)

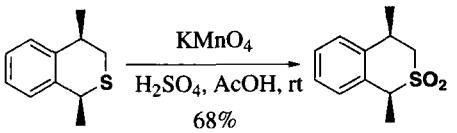
m-Chloroperbenzoic acid (*m*-CPBA) is sometimes used to oxidize isothiochromans to isothiochroman-S,S-dioxide (Eq. 79).[47,48,71,74,75,93]



208a-d **209a-d** (79)

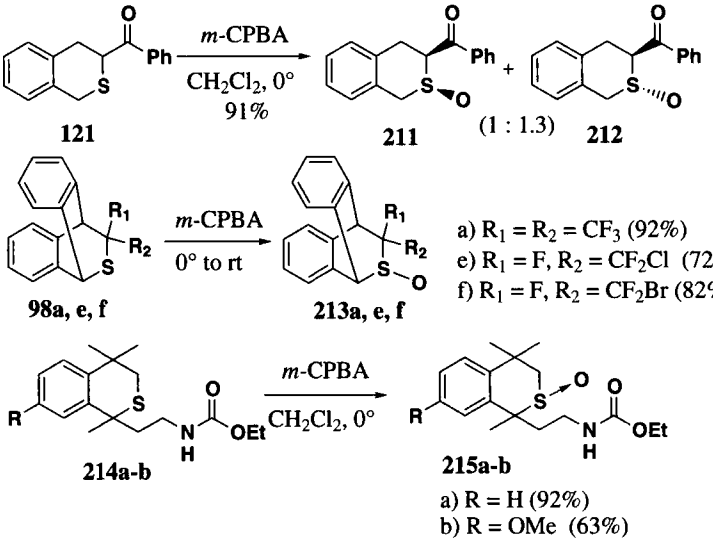
a) R_1 = H, R_2 = $CH(OMe)_2$ (78%) b) R_1 = H, R_2 = OEt (30%)
c) R_1 = H, R_2 = SEt (SO_2Et) (unspecified yield) d) R_1 = R_2 = 1,2-Ph (65%)

Potassium permanganate can also oxidize isothiochroman to isothiochroman-S,S-dioxide (Eq. 80).[28,85]



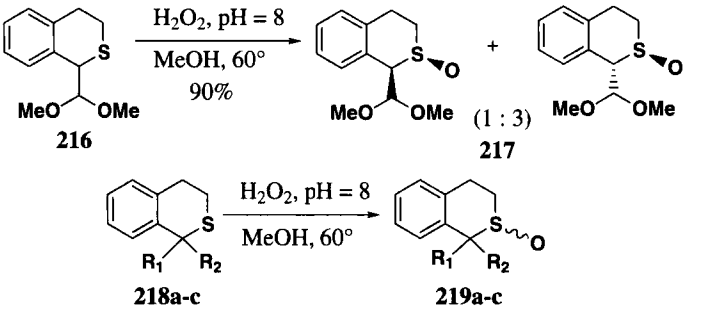
65 **210** (80)

It is possible to introduce one oxygen into the isothiochroman molecules to generate isothiochroman-S-oxides if one equivalent of oxidizing agent (*m*-CPBA) is used (Eq. 81).[16,47,48,83,99,100,102]



(81)

Under slightly basic conditions, oxidation of isothiochromans (**216, 218a-c**) by hydrogen peroxide affords to isothiochroman-S-oxides **217** and **219a-c** in a mixture of *cis*-and *trans*-isomers (Eq. 82).[65,93,94]

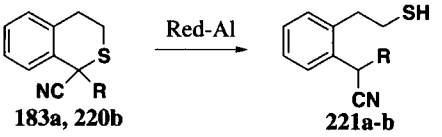


(82)

a) R_1, R_2 = H (90%) b) R_1 = Me, R_2 = CH_2NH_2 (45%) c) R_1 = Me, R = CN (45%)

b. Reduction

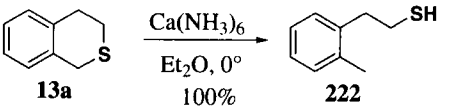
Reduction of cyano substituted isothiochromans **183a, 220b** with sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al) provides acyclic mercapto derivatives **221a-b**. The bond between the sulfur atom and the C-1 carbon is selectively reduced (Eq. 83).[93]



(83)

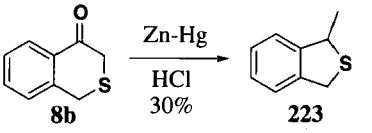
a) R = Me (45%) b) R = *i*-Pr (40%)

Calcium hexamine reduces isothiochroman **13a** cleanly to 2-(*o*-tolyl)-ethylmercaptan **222** (Eq. 84).[104]



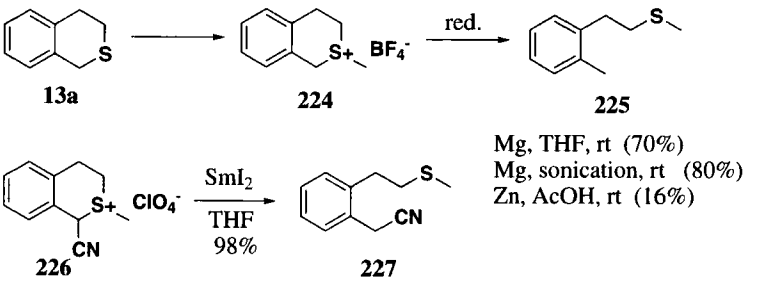
(84)

Clemmensen reduction of isothiochroman-4-one **8b** gives 1-methyl-1,3-dihydrobenzo[*c*]-thiophene **223** (Eq. 85).[105]



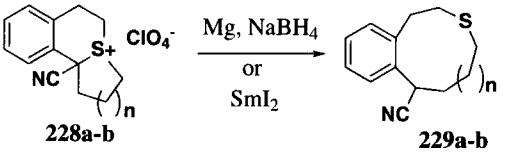
(85)

The sulfonium salt **224**, obtained from isothiochroman **13a**, is readily reduced to acyclic analog **225** by reducing agents including magnesium metal in THF and zinc in acetic acid.[106,107] SmI^2 is also a very effective reducing agent for the transformation of sulfonium salt **226** to acyclic derivative **227** (Eq. 86).[108] Again, only the bond between the sulfur atom and the C-1 carbon is reduced, no cleavage of the other carbon-sulfur bond is observed in these cases.



(86)

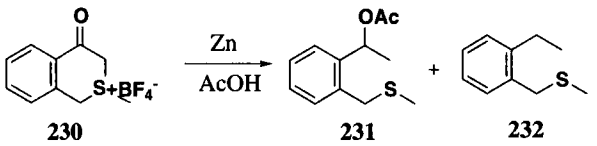
This reduction of the isothiochroman-based sulfonium salt was successfully applied to the synthesis of medium-sized cyclic sulfides by Kataoka and co-workers. For example, the reaction of tricyclic sulfonium salts **228a-b** with either $Mg/NaBH_4$ or SmI_2 afforded 9- and 10-membered bicyclic sulfides **229a-b** in good yields (Eq. 87).[108,109]



(87)

a) n = 1 (99%) b) n = 2 (unspecified yield)

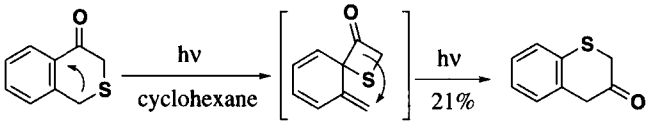
Introduction of a carbonyl functional group at the C-4 position of isothiochroman changes the pattern of this sulfonium salt reduction. Instead of the breakage of the bond between the sulfur and C-1 atom, the S-C3 bond is reduced due to the carbonyl activation. Reaction of sulfonium salt **230** with zinc in acetic acid, for example, gives exclusively the S-C3 bond cleavage products **231** and **232** with simultaneous reduction of the carbonyl group (Eq. 88).[107]



230 231 232 (88)

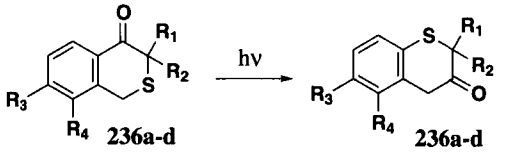
c. Rearrangement

Irradiation of isothiochroman-4-one **8b** in cyclohexane using a high pressure mercury lamp gives rise to thiochroman-3-one **234**. The reaction is proposed to occur through triene intermediate **233** *via* an 1,3-migration, followed by a second photochemically induced 1,3-rearrangement to form **234** (Eq. 89).[110]



8b 233 234 (89)

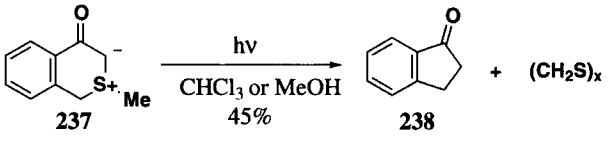
Under similar conditions, a variety of substituted isothiochroman-4-ones **235a-d** undergo the same type of rearrangement to give the corresponding thiochroman-3-one derivatives **236a-d** in moderate yield (Eq. 90).[111]



236a-d 236a-d (90)

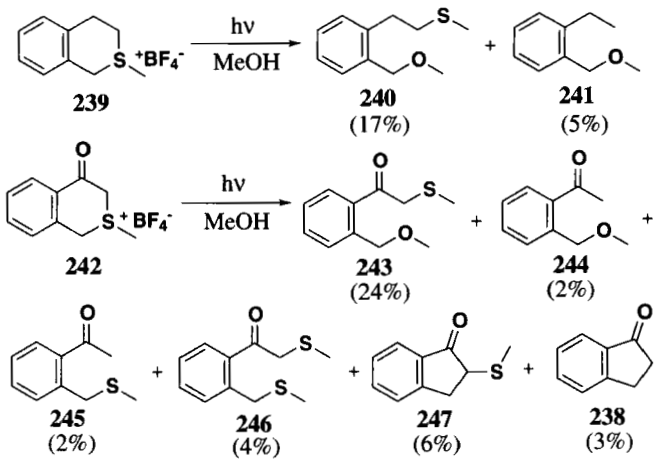
a) R_1, R_2, R_4 = H; R_3 = OMe (40% b) R_1, R_2, R_3 = H; R_4 = Me (30%)
c) R_2, R_3, R_4 = H, R_1 = Me (30%) d) R_3, R_4 = H, R_1, R_2 = Me (37%)

The photolysis of 2-methylisothiochroman-4-one-3-ylide (**237**) in either chloroform or methanol results in the ring contraction to give indanone **238** (Eq. 91).[112]



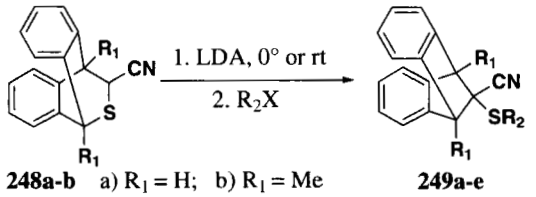
237 238 (91)

Irradiation of isothiochroman sulfonium tetrafluoroborate **239** in methanol induces ring-opening to form acyclic products **240** and **241** in low yield,[113] while the same reaction with isothiochroman-4-one sulfonium tetrafluoroborate **242** gives a complicated mixture of both cyclic and acyclic derivatives (Eq. 92).[113]



(92)

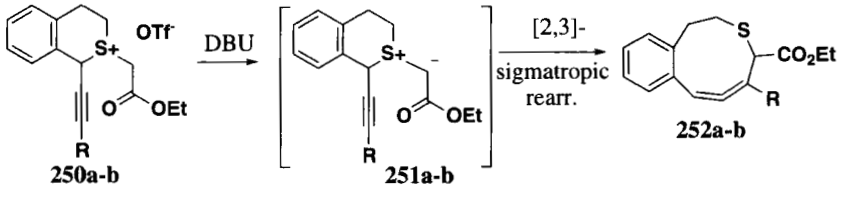
With an electron-withdrawing group such as cyano group at the 3-position, formation of a carbanion occurs readily using lithium diisopropylamide as a base. Subsequent alkylation of the resulting carbanion with a variety of electrophiles leads to ring-contracted products **249a-e**. A Wittig rearrangement has been proposed to account for the formation of these products (Eq. 93).[114]



(93)

a) R_1 = Me, R_2 = Me (70%)
b) R_1 = Me, R_2 = CH_2CN (55%)
c) R_1 = Me, R_2 = H (64%)
d) R_1 = H, R_2 = CH_2CN (52%)
e) R_1 = H, R_2 = Me (33%)

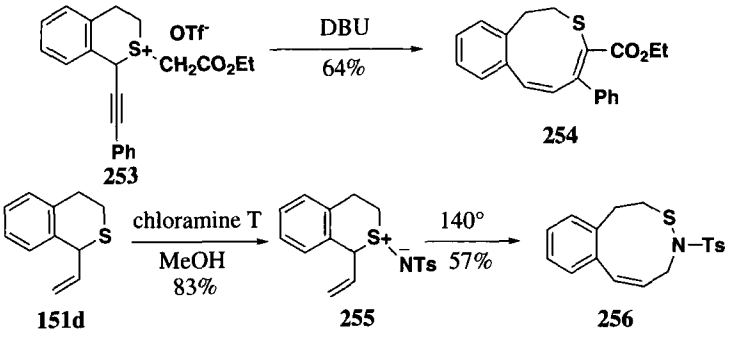
Treatment of isothiochroman sulfonium salts **250a-b** with DBU at room temperature forms stable allenic compounds **252a-b** in good yields. This three-carbon ring enlargement may involve the initial formation of sulfonium ylides **251a-b** induced by DBU, followed by a [2,3]-sigmatropic rearrangement of the ylides to give the 9-membered ring products **252a-b** (Eq. 94).[77]



(94)

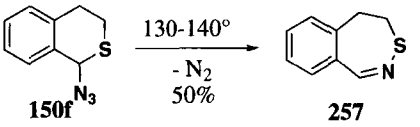
a) R = Me (60%) b) R = *n*-Bu (80%)

A very similar reaction of isothiochroman sulfonium salt **253** with DBU gives a ring-expanded product **254** with 1,3-diene functionality in the structure.[77] This ring-expansion reaction can be also applied to 1-vinylisothiochromans[78] and 1-phenylisothiochromans.[85] For example, the reaction of 1-vinylisothiochroman **151d** with chloramine T in methanol yields isothiochroman sulfonium *p*-toluenesulfonylimide **255**, which undergoes thermal rearrangement at 140° to give ring-expanded product 3,4-benzothiazonine **256** (Eq. 95).[78]



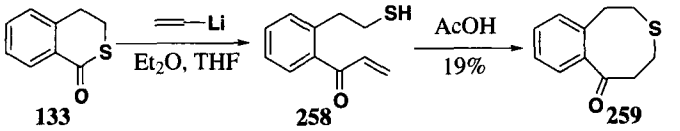
(95)

Thermolysis of isothiochroman-1-yl azide **150f** gives 4,5-dihydro-3,2-benzothiazepine **257** (Eq. 96).[75]



(96)

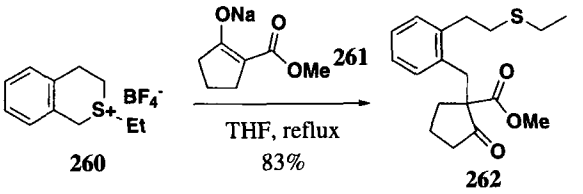
Reaction of isothiochroman-1-one **133** with vinyllithium gives a mercapto ketone intermediate **258**, which cyclizes under acidic conditions to form an 8-membered ring product **259** (Eq. 97).[66]



(97)

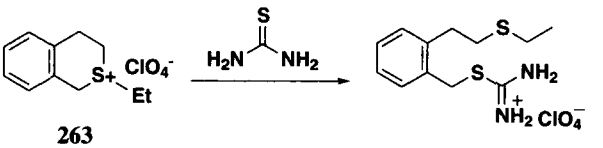
d. Substitution Reactions

The reaction of sulfonium salt **260** with the sodium enolate of β-ketoester **261** leads to the formation of acyclic product **262** in good yield (Eq. 98). The product is formed through a nucleophilic substitution of the sodium enolate at the electrophilic C-1 carbon of the isothiochroman.[115]



(98)

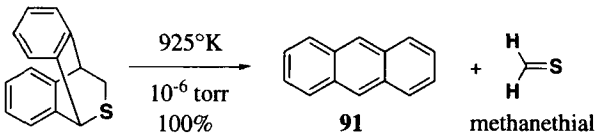
A similar type of reaction was reported using sulfur as a nucleophile. For example, reaction of sulfonium salt **263** with thiourea in DMSO gave S-alkylated product **264** (Eq. 99).[116]



263 **264** (99)

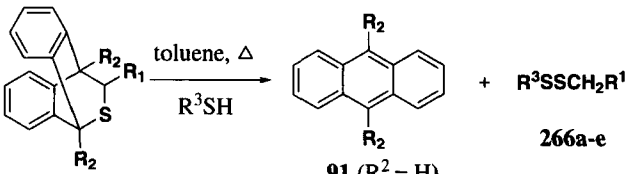
e. Retro Diels-Alder Reactions

Flash vacuum pyrolysis of isothiochroman **106a** at 925°K generates anthracene **91** and methanethial in good yield (Eq. 100).[117]



106a **91** methanethial (100)

Some substituted isothiochromans **265a-e** can undergo a similar type of retro Diels-Alder reaction in refluxing toluene in the presence of thiol. This reaction provides an interesting method to prepare asymmetrical disulfides **266a-e** (Eq. 101).[118]

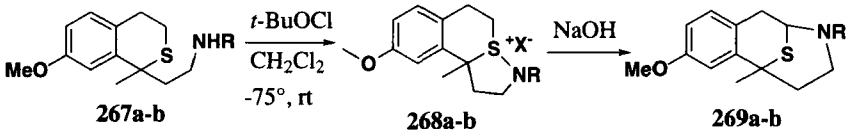


265a-e **91** (R^2 = H) **109** (R^2 = Me) **266a-e** (101)

a) R_1 = CN, R_2 = H, R_3 = *i*-Pr (75%) b) R_1 = CO_2Et, R_2 = H, R_3 = *t*-Bu (55%)
c) R_1 = CO_2Et, R_2 = Me, R_3 = *t*-Bu (90%) d) R_1 = CO_2Et, R_2 = Me, R_3 = *n*-Pr (52%)
e) R_1 = CO_2Et, R_2 = Me, R_3 = $(CH_2)_5$Me (90%)

3. Reactions at the C-3 Carbon Atom of Isothiochromans

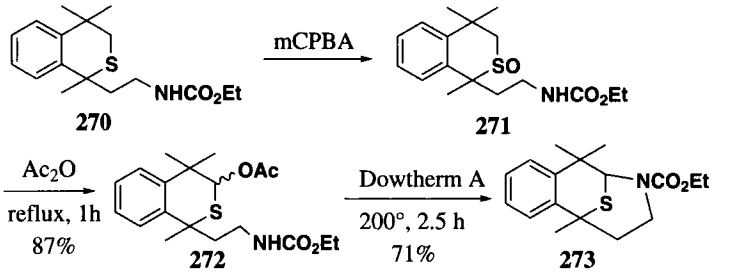
Direct functionalization at the 3-position of the simple isothiochroman system has not been well studied. However, it is possible to introduce a functional group at 3-position by intramolecular reaction. Cyclic aminosulfonium salts **268a-b**, obtained from the corresponding acyclic precursor **267a-b**, can be converted to C-3 functionalized isothiochroman analogs **269a-b** by treatment with NaOH (Eq. 102).[17]



267a-b **268a-b** **269a-b** (102)

a) R = H (27%) b) R = Me (16%)

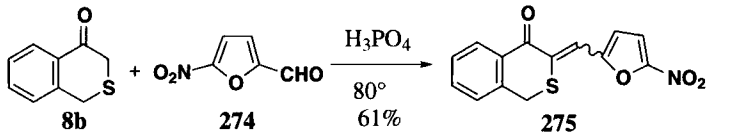
Another approach to functionalize the C-3 carbon, explored by the same research group, uses a Pummerer reaction on an isothiochroman-S-oxide. Treatment of isothiochroman **270** with *m*-chloroperbenzoic acid gives sulfoxide **271** in a 1:1 ratio of two diastereoisomers. In refluxing acetic anhydride, **271** is smoothly converted to 3-acetoxyisothiochroman **272**. Compound **272** has been successfully transformed into tricyclic benzazocine analog **273** in good yield (Eq. 103).[16,83]



(103)

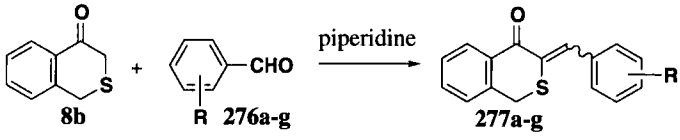
The reactivity of the 3-position of the unsubstituted isothiochroman, however, can be significantly increased by introduction of a carbonyl group at the 4-position. The remainder of this section will deal primarily with isothiochroman-4-ones.

Under acidic conditions, the condensation of isothiochroman-4-one **8b** with aldehyde **274** gives, upon elimination of water, C-3 functionalized isothiochroman **275** (Eq. 104).[119]



(104)

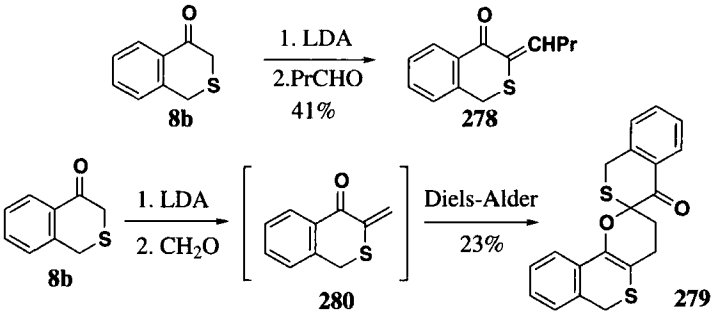
The same type of condensation was also reported to proceed under basic conditions. For example, the reaction of isothiochroman-4-one **8b** with a variety of aromatic aldehydes **276a-g** in the presence of piperidine gave rise to the α,β-unsaturated ketones **277a-g** in good yield (Eq. 105).[120]



(105)

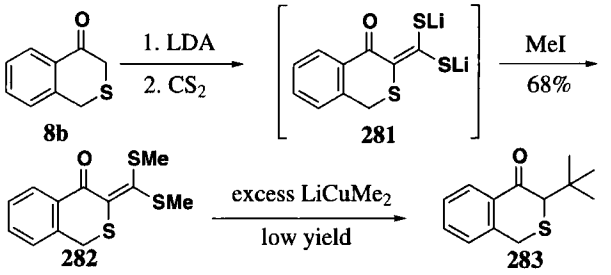
a) R = H (80%) b) R = *p*-OMe (90%) c) R = *p*-Cl (93%)
d) R = 3,4-(OCH_2O) (96%) e) R = *p*-NO_2 (80%) f) R = *p*-NMe_2 (90%)
g) R = 3,4-$(OMe)_2$ (84%)

Aliphatic aldehydes can undergo the same aldol condensation reaction with LDA as a base. For example, treatment of isothiochroman-4-one **8b** with LDA followed by addition of butyraldehyde gives 3-butylidene derivative **278** in moderate yield.[121] Interestingly, the reaction of isothiochroman **8b** with formaldehyde forms a spiro dimeric isothiochroman **279**, which is formed through a Diels-Alder reaction of the initial aldol condensation product **280** (Eq. 106).[121]



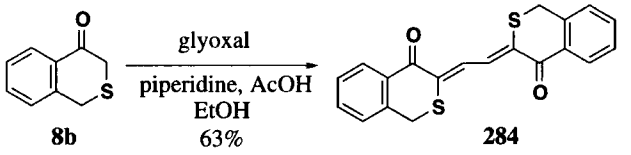
(106)

The same lithium enolate can also react with carbon disulfide to form dilithium intermediate **281**. Alkylation on the sulfur atoms with iodomethane leads to the formation of α-dithiomethylidene derivative **282** in 68% overall yield. Upon treatment with excess lithium dimethylcuprate, compound **282** is converted to 3-(*t*-butyl)isothiochroman-4-one (**283**), formed through consecutive 1,4-additions and eliminations (Eq. 107).[122]



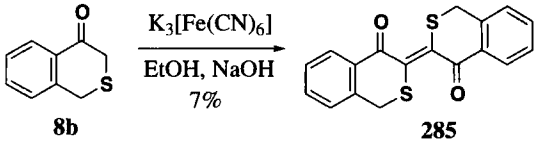
(107)

In the presence of piperidine and acidic acid, the reaction of isothiochroman-4-one **8b** with glyoxal leads to the dimeric structure **284** (Eq. 108).[123]



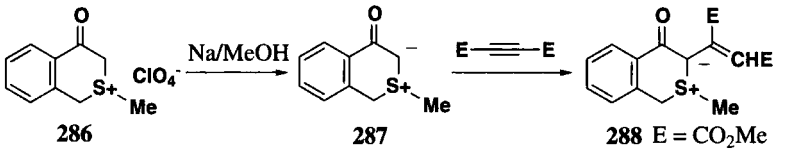
(108)

Treatment of isothiochroman-4-one **8b** with $K_3[Fe(CN)_6]$ promotes oxidative dimerization to **285** (Eq. 109).[123]



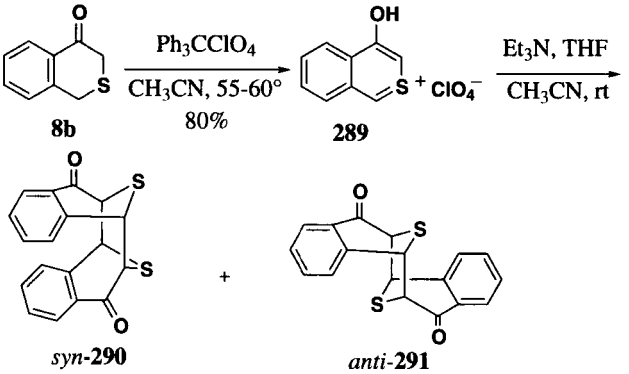
(109)

Sulfonium ylide **287**, obtained form the reaction of sulfonium salt **286** with sodium methoxide, undergoes a 1,4-nucleophilic addition with dimethyl acetylenedicarboxylate to form a new stable ylide **288** in 72% yield (Eq. 110).[124]



(110)

Perchloric acid salt of 2-benzothiopyrylium-4-olate **289**, obtained from the reaction of isothiochroman-4-one **8b** and triphenylmethyl perchlorate, is readily dimerized to give *syn*-stereoisomer **290** and *anti*-stereoisomer **291**.[125] Other analogs of **289** with a methyl substituent at either 1- or 3-position give similar dimerized products when treated with triethylamine (Eq. 111).[126]

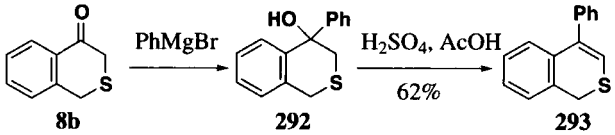


(111)

4. Reactions at the C-4 Carbon Atom of Isothiochroman-4-ones

The reactions at the C-4 carbon atom summarized in this section are very similar to the reactions at the C-3 carbon of isothiochroman described previously and are limited to isothiochroman-4-one systems. To the best of this author's knowledge, no chemistry at the 4-position of unsubstituted isothiochroman has ever been reported. This fact can also be attributed to the lower reactivity of this position in comparison to the reactivity of the activated C-1 carbon.

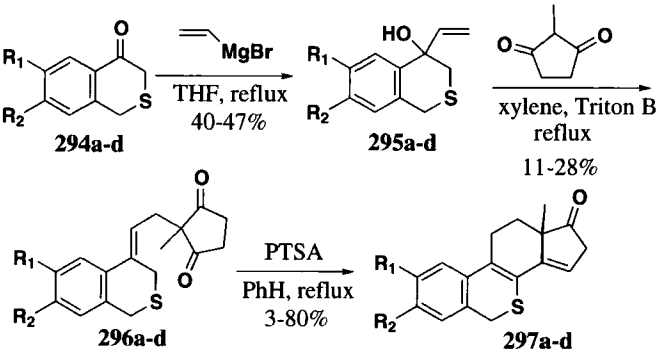
As expected, the electrophilic carbonyl group of isothiochroman-4-one can be attacked by nucleophiles to form addition products. For example, the reaction of **8b** with phenylmagnesium bromide gives 4-hydroxyl-4-phenylisothiochroman **292**. Upon treatment with acid, the carbanol derivative **292** undergoes dehydration to form 4-phenylisothiochromen **293** in moderate yield (Eq. 112).[127]



(112)

Reaction of vinylmagnesium bromide with several substituted isothiochroman-4-ones **294a-d** leads to the 4-hydroxyl-4-vinyl isothiochroman derivatives **295a-d** in yields ranging from 40 to 47%. The derivatives **295a-d** serve as important synthons for the synthesis of 7-heterosteroids. For example, refluxing **295a-d** with 2-methylcyclopentane-1,3-dione and Triton B in xylene gives *seco*-steroids **296a-d**. Cyclodehydration of the *seco*-steroids **296a-d** with *p*-toluenesulfonic acid in benzene

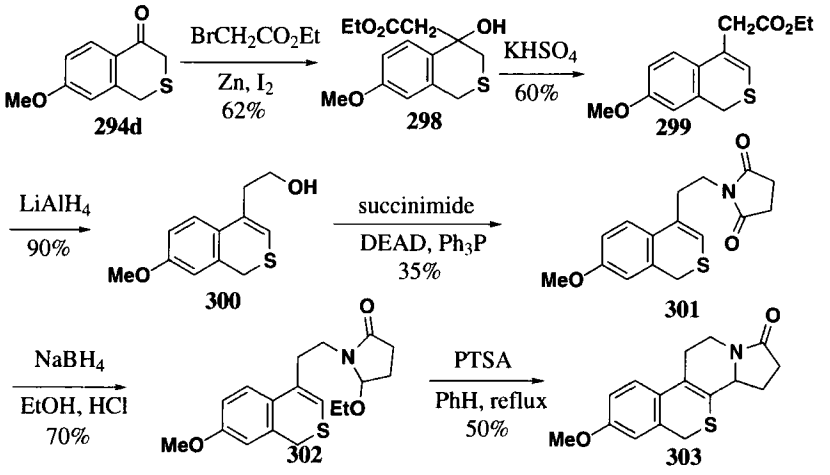
furnishes substituted 17-oxo-7-thia-1,3,5(10)8,14-estrapentaenes **297a-d** (Eq. 113).[128]



(113)

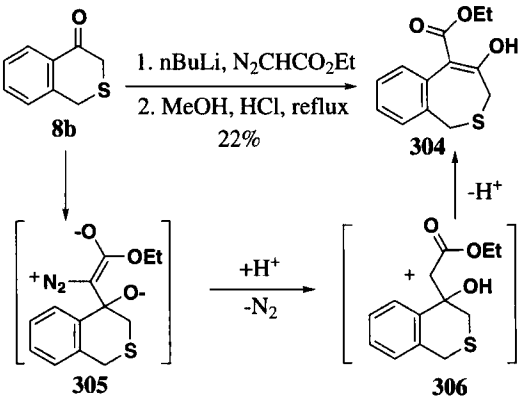
a) R_1 = Me; R_2 = H b) R_1, R_2 = H c) R_1 = H; R_2 = Me d) R_1 = H; R_2 = OMe

Reformatsky reaction of 7-methoxyisothiochroman-4-one **294d** with ethyl bromoacetate in the presence of zinc and iodine provides carbonyl addition product **298**. Dehydration of **298** with fused $KHSO^4$ affords isothiochromen derivative **299**, which has been successfully converted to tetracyclic structure **303** in a 4-step sequence in good overall yield as shown in the equation (Eq. 114). Compound **303** is a heteroatom-containing analog of estrogen, which may possess therapeutic activity.[129]



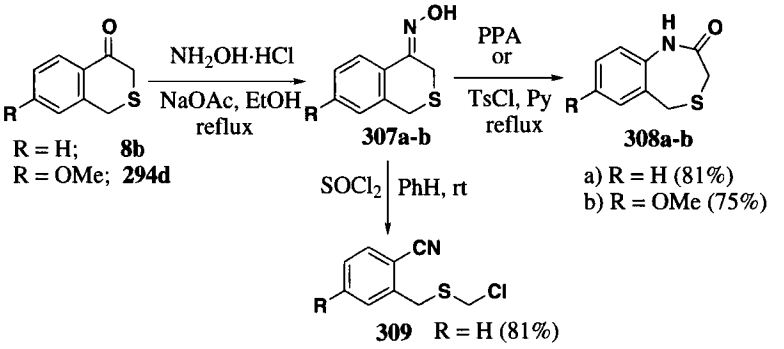
(114)

Like other cyclic ketones, isothiochroman-4-one can undergo ring expansion reaction with diazoalkanes. For example, treatment of isothiochroman-4-one **8b** with ethyl diazo(lithio)acetate followed by addition of methanolic hydrogen chloride gives ethyl 1,3-dihydro-4-hydroxy-2-benzothiepin-5-carboxylate **304** in 22% yield.[130] The ring homologation reaction involves initial nucleophilic addition of ethyl diazo(lithio)acetate to the carbonyl functionality to form α-diazo-β-hydroxyester **305**, which then decomposes with loss of nitrogen to give cationic intermediate **306**. 1,2-Migration of the phenyl group and the loss of a proton gives rise to the ring expanded product **304** (Eq. 115).



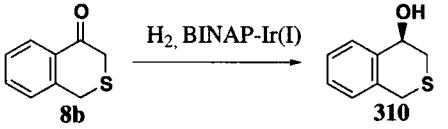
(115)

Reactions of isothiochromans **8b** and **294d** with hydroxylamine affords oxime derivatives **307a-b** in good yields. Beckmann rearrangement of **307a-b** in the presence of PPA or tosyl chloride and pyridine results in the formation of seven-membered ring lactams **308a-b**.[131,132] Treatment of oxime **307a** with $SOCl_2$ in benzene gives the ring-opening product **309** (Eq. 116).[132]



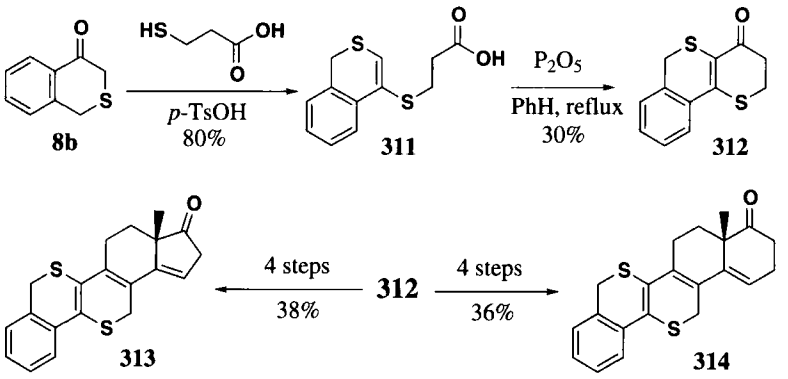
(116)

The ketone functionality of isothiochroman-4-one **8b** can be hydrogenated to give optically active secondary alcohol **310** in low to moderate enantiomeric excess by use of 2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl (BINAP)-Ir(I)-aminophosphine complexes (Eq. 117).[133]



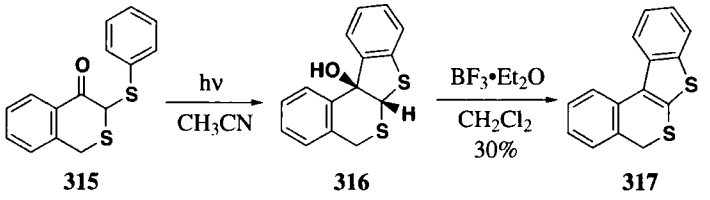
(117)

The reaction of isothiochroman **8b** with β-mercaptopropionic acid in the presence of *p*-TsOH provides *bis*-thio olefin **311** in good yield. Upon treatment with phosphorus pentoxide, compound **311** undergoes cyclodehydration to afford tricyclic ketone **312**, which is then converted to pentacyclic, heteroatom-containing steroids **313** and **314** in 4 steps with good overall yields (Eq. 118).[134-136]



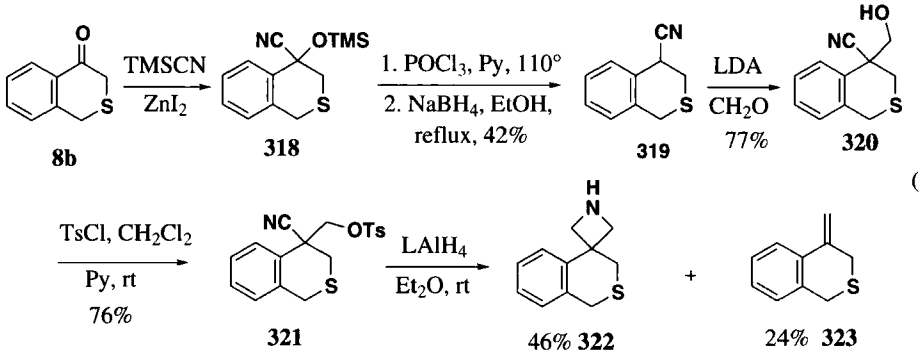
(118)

Irradiation of 3-phenylthioisothiochroman-4-one **315** in acetonitrile affords *cis*-fused tetracyclic compound **316**. A radical mechanism is proposed for this transformation. Treatment of **316** with BF_3•Et_2O in dichloromethane results in dehydration to give **317** in 30% overall yield (Eq. 119).[137,138]



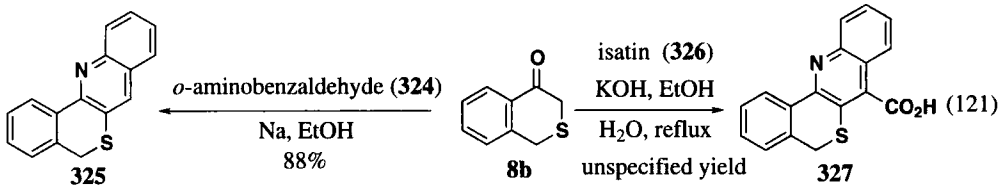
(119)

Sauter *et al.* recently reported a synthesis of 3,3-disubstituted azetidine analog **322** starting from isothiochroman-4-one **8b**. Carbonyl cyanosilylation of **8b** followed by dehydration and double bond reduction afforded 4-cyanoisothiochroman **319** in 42% overall yield. Hydroxymethylation of **319**, followed by *O*-tosylation and $LiAlH_4$ reduction of the cyano group led to 3,3-disubstituted azetine **322** *via* spontaneous cyclization of the intermediate amine. A by-product **323** was also obtained as a minor product (Eq. 120).[139]



(120)

The reaction of isothiochroman-4-one **8b** with *o*-aminobenzaldehyde **324** in the presence of sodium ethoxide gives tetracyclic product **325** in good yield. Similar reaction with isatin **326** in KOH affords **327**. Both **325** and **327** show good bacteriostatic activity (Eq. 121).[140]



III. CONCLUSION

The use of isothiochroman as a bioisostere for natural bicyclic systems in medicinal chemistry to improve biological activity, coupled with the interest of chemists in the structure and reactivity of this heterocyclic system, has resulted in a rapid growth of isothiochroman chemistry in recent years. Many new synthetic methods for the preparation of isothiochromans have been discovered. New reactions to modify existing isothiochromans to more functionalized isothiochromans have been developed. In turn, this new chemistry will allow chemists to prepare more elaborated isothiochroman analogs for their structure activity relationship studies. With the existing examples of the successful use of isothiochromans in structure activity relationship studies,[2a-m] the further growth in isothiochroman chemistry is surely guaranteed.

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