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Recent Advancement of the thio-Claisen Rearrangement[#]

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Abstract: This brief review deals with the recent progress in the implimentation of thio-Claisen rearrangement in synthetic organic chemistry. Thio-Claisen rearrangement has been utilized for the synthesis of many heterocyclic moieties of biological significance. Stereoselectivity of the thio-Claisen rearrangement has also been discussed. This short report mainly covers the literature published during 2003 onwards.

Keywords: Thio-Claisen rearrangement, thermal Claisen-rearrangement, catalyzed-Claisen rearrangement, asymmetric rearrangement, sulfur heterocycles, regioselective synthesis, stereoselective synthesis, electrocyclization, [3,3]-sigmatropic shift, cyclodextrin, dihydroflustramine C, sequential Claisen rearrangement, $[Rh_2((S)\text{-tbsp})_4]$.

1. INTRODUCTION

The discovery of the Claisen rearrangement almost a century ago [1] offered a potentially useful tool for the formation of carbon-carbon bonds [2-6] and synthesis of heterocyclic compounds to the organic chemists. Over the decades this usefulness has been realized and the reaction has drawn the attention of numerous research groups. The first appearance of the thio-Claisen rearrangement (TCR) in the literature occurred in 1962 [7]. Among the various ways of formation and chemical transformations of organic compounds of divalent sulfur, the thio-Claisen rearrangement which occurs at elevated temperature in the absence of a catalyst or promoter, takes a special place. The TCR is the sulfur analogue of the simple Claisen rearrangement [1, 8-11]. The [3,3] sigmatropic rearrangement of allyl and vinyl sulfides [12-17] generally takes place under mild condition leading to good yields of γ-unsaturated thiocarbonyl compounds. The facile nature of the transformation, as compared to the oxygen and nitrogen series, is mainly of kinetic origin [18] and is explained by the cleavage of the C-S bond being easier relative to the C-O and C-N bonds. However, thio-Claisen rearrangement of allyl phenyl sulfides require higher temperature to produce the corresponding thiols. We have attempted to discuss the recently published results and some examples which were not included in detail in previous reviews [12, 19-23].

2. MECHANISTIC ASPECT

The DFT calculations, NICS study, and NBO analysis created a reasonable picture from structural, energetic, and bonding points of view for the Claisen rearrangement of 3-(vinyloxy)prop-1-ene and the thio-Claisen rearrangement of allyl vinyl sulfide. Based on the results, Zahedi *et al*. [24] concluded that the chair-like transition state of the thio-Claisen rearrangement has higher diatropic current with respect to the Claisen rearrangement. Aromaticities of the transition states are controlled by the out-of-plane component of isotropic chemical shift. The resonance energies in allyl vinyl sulfide are higher than 3-(vinyloxy)prop-1-ene, and the σ_3-4 bonding orbital occupancy in allyl vinyl sulfide is less than 3-(vinyloxy)prop-1-ene. The HOMO-LUMO gap decreases in accor dance with increase of the electronic delocalizations from σ_3-4 bonding orbital to antibonding orbitals. In the 3-(vinyloxy)prop-1-ene and allyl vinyl sulfide rearrangements, activation energies are controlled by the resonance effects (Fig. (**1**)).

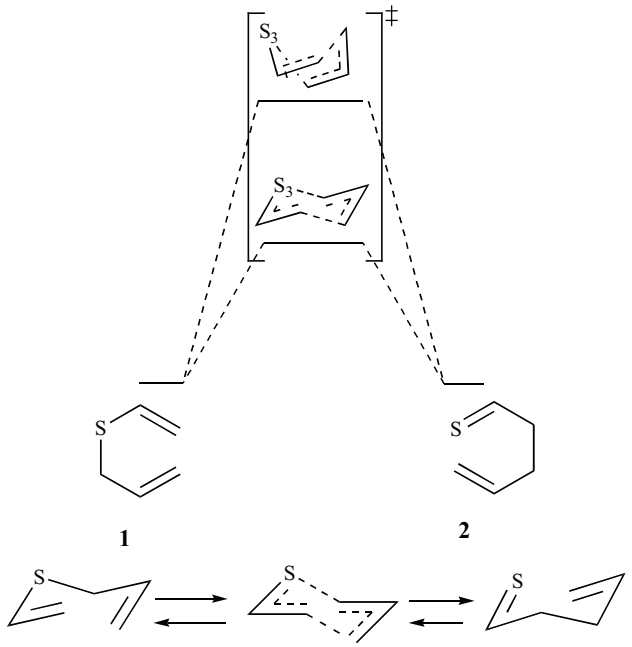

Fig. (1). The thio-Claisen rearrangements *via* two pathways (chair-like and boat-like).

3. STEREOSELECTIVE SYNTHESIS

Thio-Claisen rearrangement also gives excellent opportunities for the synthesis of new carbon skeletons with high stereoselectivity [25] in comparison to the other Claisen-type rearrangements.

The piperidine ring is a common structural building fragment occurred in many natural compounds and their synthetic analogues [26]. Until now most common approaches to piperidine-cyclopentane fused systems were based on the initial stereoselective

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[#]A tribute to 100 years of the Claisen rearrangement

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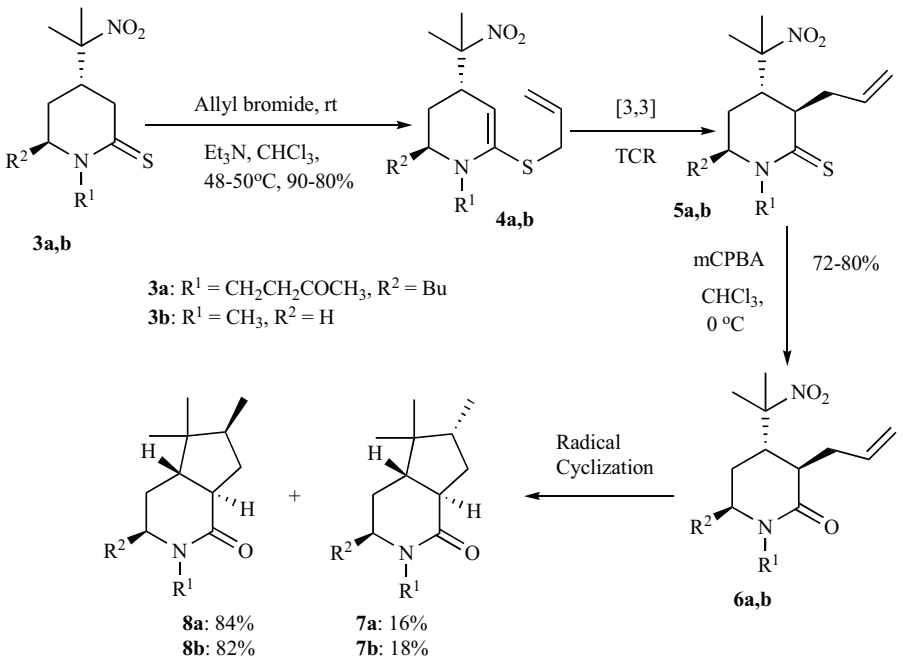
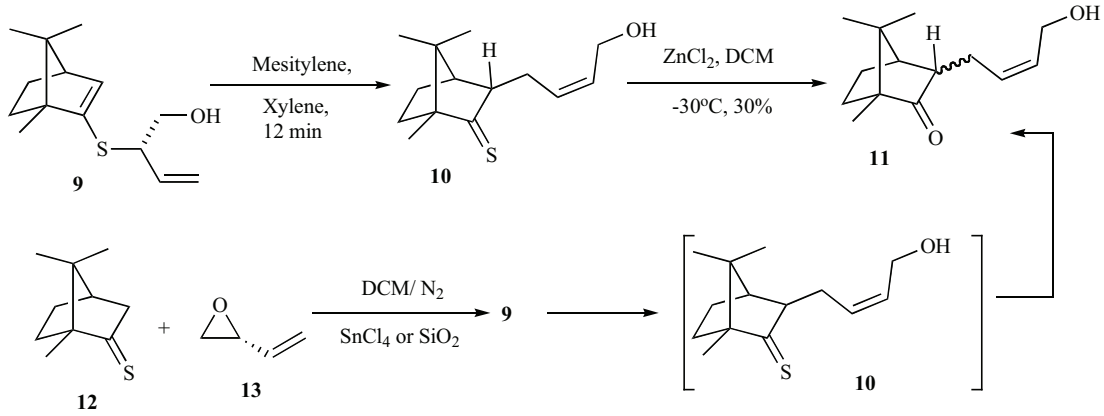


Scheme 1. Synthesis of bicyclic 2-piperidinone derivatives *via* asymmetric thio-Claisen Rearrangement.



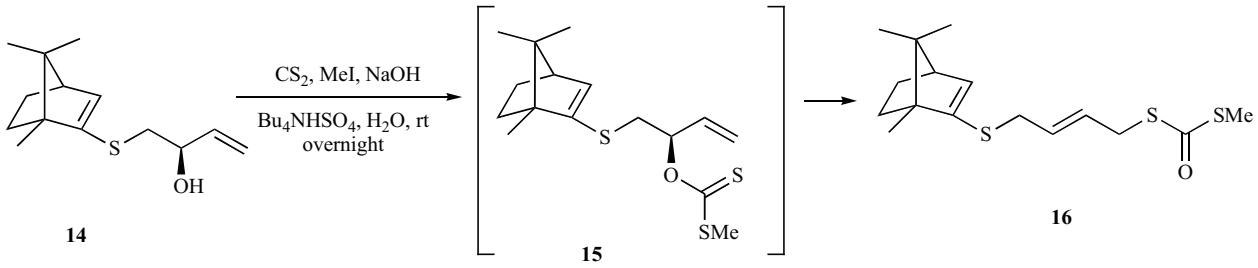
Scheme 2. [3,3]-Sigmatropic rearrangement of *S*-allylthiocamphor.

synthesis of substituted cyclopentane ring annulation by aza-heterocyclization [27]. Sosnicki *et al*. recently synthesized some piperidine ring containing compounds **7** and **8** by the implementation of the thio-Claisen rearrangement [28] starting from thiolactams **3**. The S-allylation products formed in the reaction of **3** with allyl bromide were isolated as salts and the subsequent thio-Claisen rearrangement was conducted under mild conditions with triethylamine in chloroform adopting a known protocol [29]. The resulting 3-allyl-piperidine-2-thiolactones **5a** and **5b** were obtained in high yields. Because of the instability of thiocarbonyl group in the radical reaction, the thiolactams were transformed into the corresponding lactams in an oxidative manner using mCPBA. Finally the desired piperidine moieties were constructed by the radical-mediated cyclization (Scheme **1**) [30].

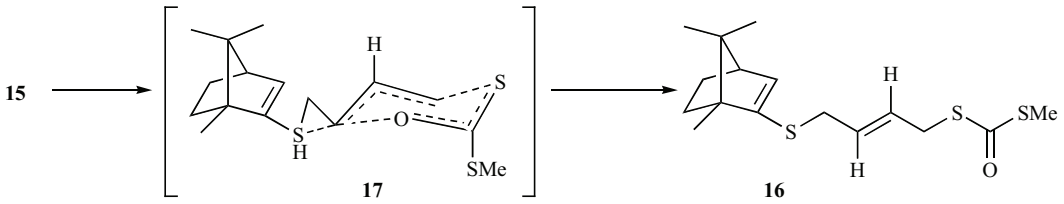
Heimgartner and Fu have recently shown that thio-Claisen rearrangement of the compound **9** in boiling mesitylene led to the formation of the alcohol **10** in 88 % yield. Treatment of the resulting alcohol **10** with $ZnCl_2$ in CH_2Cl_2 under a nitrogen atmosphere at -30 °C for 3 h gave the corresponding dethionated product **11** in 30 % yield. The dethionated alcohol **11** may also be obtained when the thiocamphor **12**, and 2-vinyloxirane were allowed to react in the presence of mild Lewis acidic catalysts $SnCl_4$ or SiO_2 in CH_2Cl_2 under a nitrogen atmosphere. The yield of the dethionated product **11** was poor. The mechanistic pathway for the formation of the product may be explained by considering initial reaction of thiocamphor **12** with 2-vinyloxirane **13** to produce the precursor **9** for subsequent thio-Claisen rearrangement. The compound **9**, may undergo a [3,3] sigmatropic rearrangement *in situ* to afford the intermediate compound **10** which may afford the dethionated alcoholic product **11** under the reaction condition (Scheme **2**) [31].

Moreover, the same group have also reported an interesting thio-Claisen rearrangement of the substrate **15**. The substrate **15** was prepared from the compound **14** by the treatment of 5 equiv. of MeI in a two-phase system of 50 % aq. NaOH containing 0.1 equiv. of Bu_4NHSO_4 and 2.2 ml of CS_2 at rt for overnight. Interestingly, under this reaction condition the product **16** was formed in 81 % yield *via* a [3,3]-sigmatropic rearrangement of the intermediate xanthate **16** (Scheme **3**) [31].

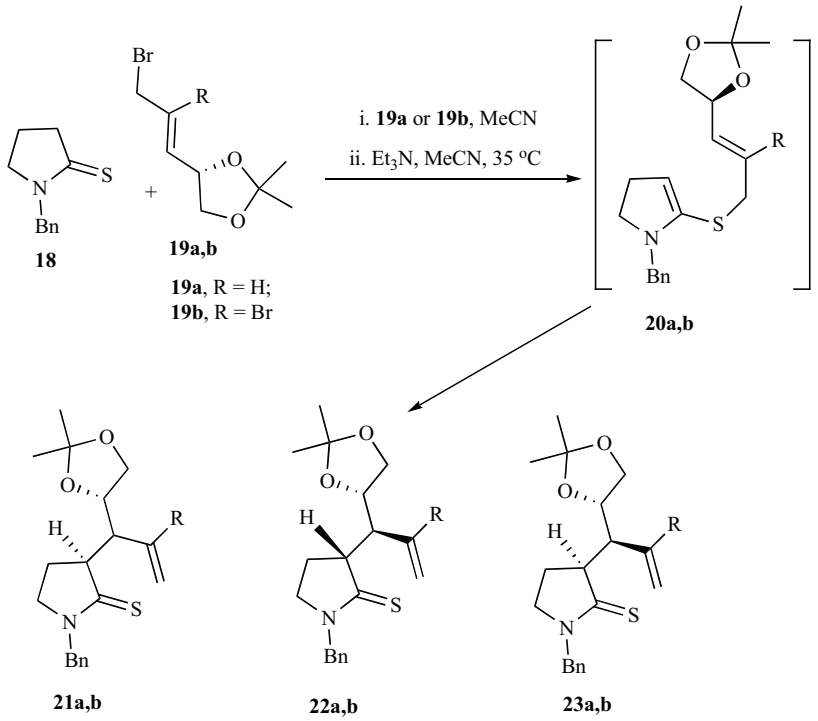
The rearrangement of the allylic xanthates is known to proceed thermally (ca. 100°C) *via* a concerted reaction [32] mechanism ([3,3]-sigmatropic rearrangement). Experimentally it has been found that the reaction can be accelerated by catalysis with *β*-cyclodextrin, in which case the reaction occurs in an inclusion complex [33] at 2-5 °C. The generation of the dithiocarbonate **16**



Scheme 3. Preparation of thio-Claisen precursors.



Scheme 4. Spacial orientation of the transition state.



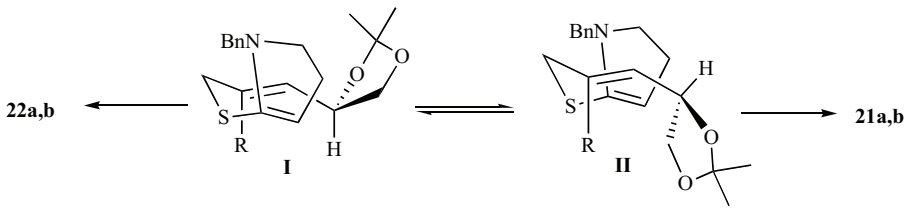
Scheme 5. Product ratio in thio-Claisen rearrangement

Entry	Bromide	Ratio **21**:**22**:**23**	Yield of **21**(%)	Yield of **22**(%)	Yield of **23**(%)
1	**20a**	2.5:1:0.1	38	10	1
2	**20b**	1:12.2:0.6	2	52	2

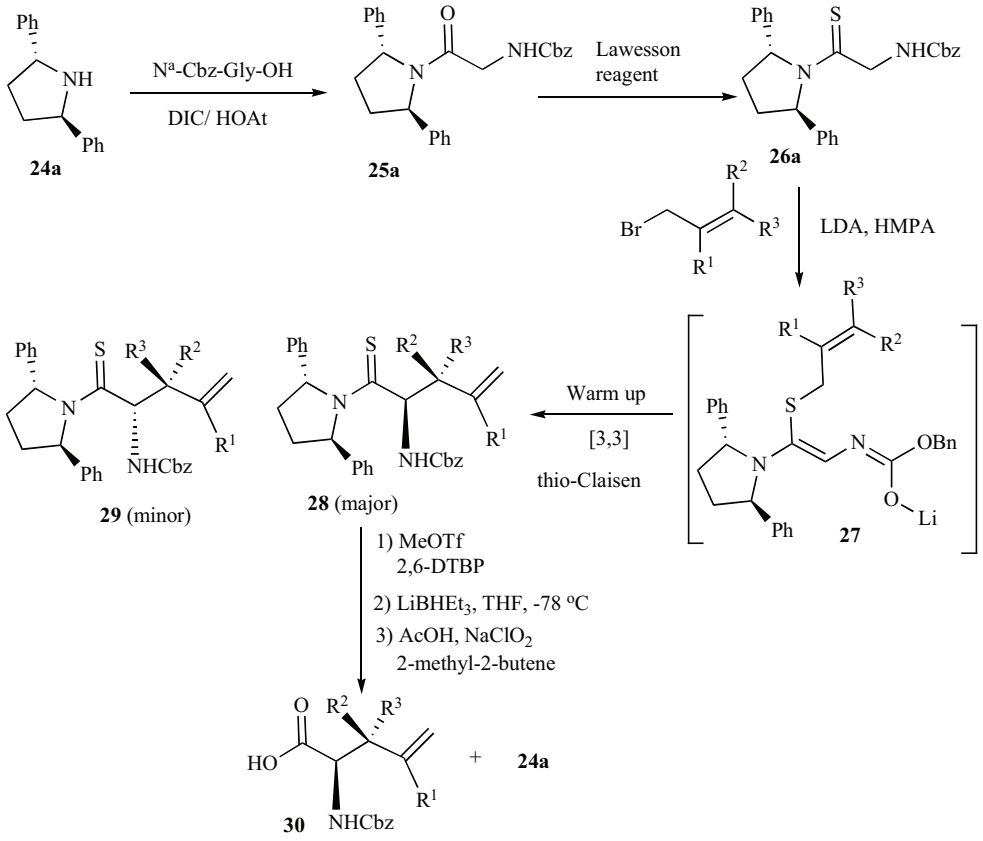
Scheme 5. Product ratio in thio-Claisen rearrangement.

via the intermediate **15** occurs stereospecifically and smoothly *in situ* at room temperature. A concerted mechanism ie. a [3,3]-sigmatropic rearrangement is postulated *via* the transition state '**17**', in which a neighbouring group participation is responsible for the acceleration of the reaction (Scheme **4**).

Another example of thio-Claisen rearrangement was observed during the synthesis of the core of Sarain Alkaloids [34]. Initially, the alkylation of *N*-benzylpyrrolidine-2-thione (**18**) with bromide **19a** was followed by deprotonation with triethylamine in acetonitrile giving the transient intermediate **20a** which *via* thio-Claisen rearrangement afforded a mixture of thiolactams **21a**, **22a** and **23a**, three of the four possible stereoisomeric products (Scheme **5**) [35]. The major products were the expected isomers **21a** and **22a**, arising from a chair transition state, with only a small amount of a third diastereomer **23a**. Very poor diastereoselectivity (2.5:1) of this rearrangement proved a low level of facial selectivity imparted



Scheme 6. Proposed reactive conformations of **20a** (R = H) and **20b** (R = Br).



Scheme 7. Generation of thio-enolate dianion and asymmetric thio-Claisen rearrangement.

upon the *exo*cyclic double bond by the adjacent stereocentre in **20a**. It could be due to the presence of more than one significantly populated rotamer about the bond between the alkene and the stereogenic centre.

The stereochemistry of this reaction can be explained by considering the reactive conformations of intermediates **20a** and **20b**. If it is assumed that (i) the reaction takes place through a chair transition state, and that (ii) reaction of the 'nucleophilic' *N*,*S*-ketene acetal fragment on the 'electrophilic' allyl sulfide fragment occurs *anti* to the allylic oxygen substituent, then two possible reactive conformations can be drawn, these are depicted as **I** and **II** in Scheme **6**. Conformation **I** gives rise to the products **22a** and **22b** while conformation **II** leads to the products **21a** and **21b**.

Optically active nonproteinogenic amino acids are very important in the development of peptides and peptidomimetics as therapeutic agents [36]. Among these *β*-substituted *γ*,*δ*-unsaturated amino acids have become magnificent building blocks for these studies due to the variation in reactivities of the terminal double bond and their ability to introduce biologically active functionalities [37]. Claisen rearrangement [38] is one of the most powerful synthetic methods toward the construction of this type of structural skeleton. Hruby *et al*. achieved a synthesis of such amino acids *via* the Eschenmoser-Claisen rearrangement with excellent diastereoselectivity and good enantioselectivity [25f, 39]. Recently, the same group reported [40] another novel, complementary route using a bulky recyclable *C*2 symmetric chiral auxiliary *via* thio-Claisen rearrangement. The *C*2 symmetric chiral auxiliary (2*R*,5*R*)-2,5-diphenylpyrrolidine (**24a**) was prepared in optically pure form and coupled to N^{α}-Cbz glycine to generate amide **25a** using di-isopropylcarbodiimide (DIC)/7-aza-1-hydroxybenzotriazole (HO At) as the coupling reagents. This coupling reaction gave excellent yields despite steric hindrance of the phenyl rings (Scheme **7**). The compound **25a** was first thionated with Lawesson reagent and then allylated with substituted allyl bromide in the presence of LDA in THF at -78 °C. Thio-Claisen rearrangement occurred when the reaction mixture was warmed slowly to room temperature or higher (when necessary) to afford thioamides **28** and **29**. This method is straightforward and highly selective using a bulky *C*2 symmetric chiral auxiliary, and the chiral auxiliary can be recycled after producing the final amino acids.

Despite higher temperature being required in some cases in the thio-Claisen rearrangement step, the diastereoselectivities generally were excellent, and only *anti* products were obtained as expected. In many cases, only optically pure compounds were obtained (Table **1**).

Table 1. Results of Asymmetric thio-Claisen Rearrangement

Entry	Allylation Agent	*t* (°C)	anti:syn	de(%, 28/29)	Yield (%)
a	R^1= R^2= R^3= H	-78-rt	NA	>99	82
b	R^1= H; R^2= R^3= Me	-78-reflux	NA	>99	66
c	R^1= Me; R^2= R^3= H	-78-rt	NA	>99	74
d	R^1= R^2= H; R^3= Me	-78-40	>99:1	>99	78
e	R^1= R^2= H; R^3= Et	-78-40	>99:1	78	76
f	R^1= R^2= H; R^3= Ph	-78-rt	>73:1	75	65

Two possible chair-like transition states depicted **TS-A** and **TS-B** are in Fig. **(2). TS-A** is favoured over **TS-B** for steric reasons. A decrease of the diastereoselectivity was observed during the study as the size of R^3 was increased. Presumably, this was caused by the increasing steric repulsion between the Cbz group and R^3.

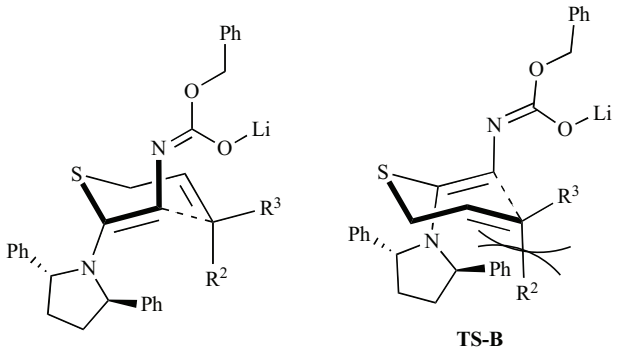
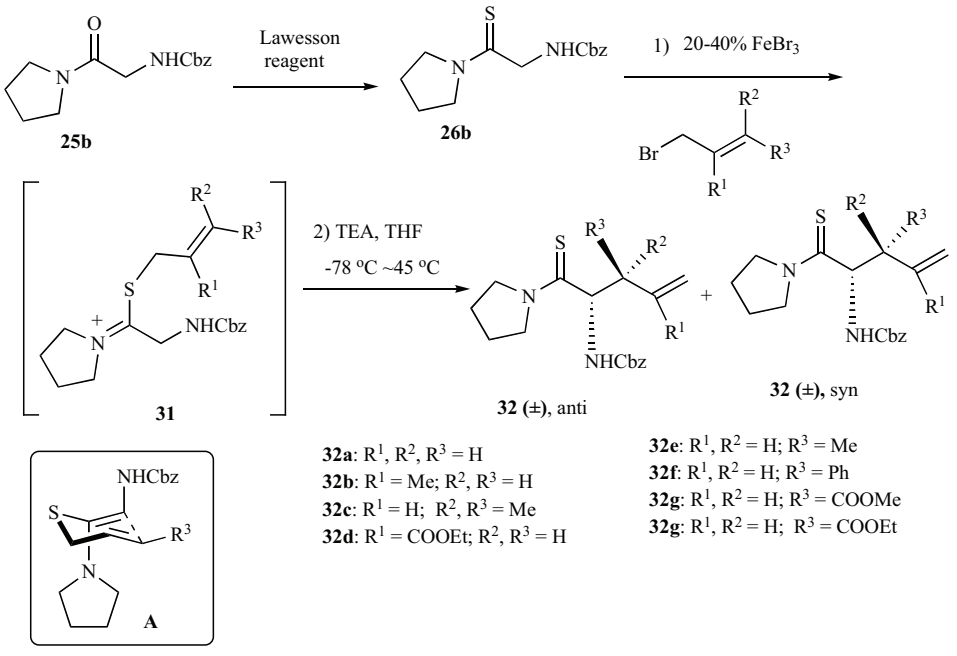


Fig. (2). Proposed transition state model of thio-Claisen rearrangement.

Very recently, the same group have also reported [41] a greatly improved thio-Claisen rearrangement reaction, which featured a $FeBr_3$-catalyzed allylation to provide more versatile amino acid derivatives and avoided the use of strong base treatment to form the enolate dianion (or equivalent) for the alkylation (Scheme **8**).

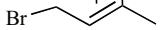
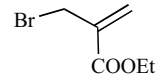
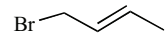
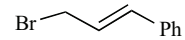
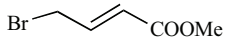
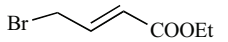
The rearrangement can be facilitated *via* the deprotonation of the α-proton from the resulting thioiminium cation (**31**) in presense of one equivalent of a weak base as compared to the multi equivalents of strong base used previously. The thio-Claisen rearrangement products **32** were isolated successfully upon adding TEA as base in a polar aprotic solvent (THF) which along with heating were supposed to accelerate the allylation process. Both $ZnBr_2$ and $FeBr_3$ gave significantly improved yields *via* a Friedel-Crafts alkylation type reaction, with $FeBr_3$ providing comparatively better yields. Good to excellent *anti*/*syn* ratios were observed due to the predominant formation of *Z*-thioenol ethers *via* the deprotonation [14] and the chair-like six-membered ring transition state [25f,40] (**A** in Scheme **8**). The ester groups were also successfully introduced into the *β*-position. Thus, this mild reaction condition have expanded the scope of different functional groups that can be introduced at the *β*-position. The *anti/syn* selectivity of thio-Claisen rearrangement utilizing various allylating reagents are summarized in table **2**.

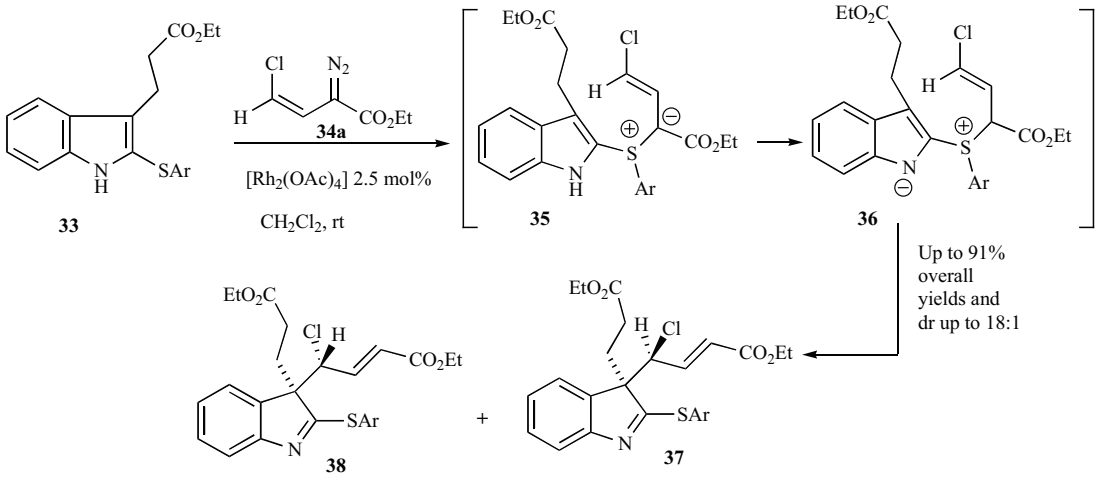
The generation of quaternary centers at C3 of oxindoles and indolines stereoselectively, is a challenging task for synthetic organic chemists [42]. Rainier *et al*. [43, 44] developed an interesting



Scheme 8. Asymmetric thio-Claisen rearrangement under mild basic condition.

Table 2. Results of thio–Claisen Rearrangement

entry	Allylation reagent	product	Anti/syn	yield
1		**32a**	n/a	68%
2		**32b**	n/a	69%
3		**32c**	n/a	42%
4		**32d**	n/a	72%
5		**32e**	10:1	74%
6		**32f**	8:1	51%
7		**32g**	>49:1	82%
8		**32h**	>49:1	72%



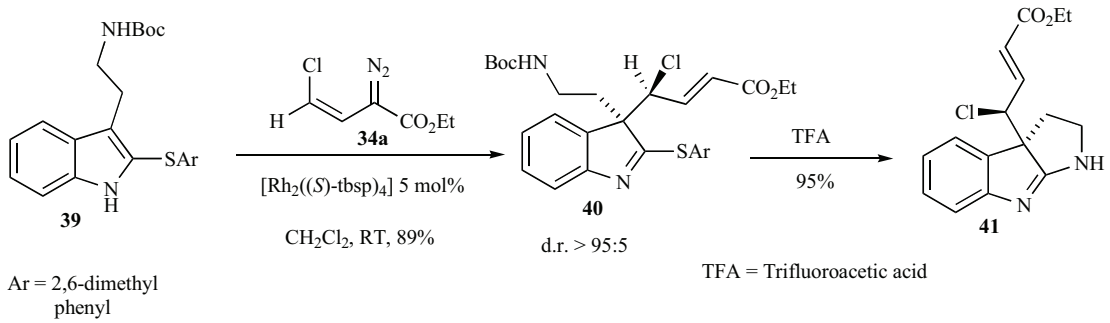
Scheme 9. Diastereoselective synthesis of quaternary substituted indoline derivates.

Table 3. The influence of Thioaryl Substitution on the Diastereoselectivity

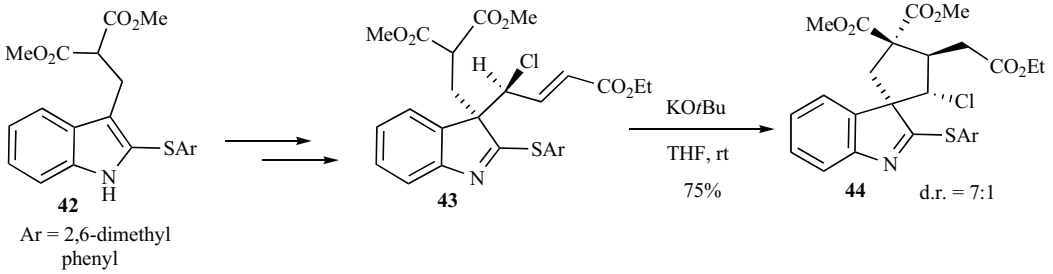
entry	indole	Ar	**37**/**38**	yield
1	**33a**	4-OMeC_6H_4	7:1	86
2	**33b**	4-$NO_2C_6H_4$	7:1	74
3	**33c**	2-OMeC_6H_4	9:1	74
4	**33d**	2-FC_6H_4	7:1	81
5	**33e**	2-MeC_6H_4	11:1	75
6	**33f**	2,6-dimethylphenyl	15:1	96
7	**33g**	2-*i*PrC_6H_4	18:1	91

method aimed at using of 2-thioindoles as precursors to substituted oxindoles and indolines. The coupling of 2-thio-3-alkylindoles with vinyl diazoacetates carried out in the presence of Rh^{II} salts is fascinating because the reaction delivers structurally rich quaternary substituted indolines in high yields and the mechanism is also interesting [44]. The reaction is not usable in the total synthesis because it is only modestly diastereoselective, when monosubstituted vinyl diazoacetates are used as the coupling partners. Recently, Rainier *et al*. [45] have described an unique, high yielding, and diastereoselective coupling reaction involving sulfonium ylide intermediates (**35** and **36**) from halogenated vinyl diazoacetates **34** and 2-thioindoles **33**. No products were isolated from the reaction of the vinyl carbenoid with indole lacking the thioether unit. The effects of substituent at the C3 of the indole were also examined and 3-*tert*-butyl-2-thiophenylindole gave the highest selectivity. Enhanced diastereoselectivity was observed in case of 2-thioarylethers (**33**) than 2-thioalkylethers (Scheme **9**).

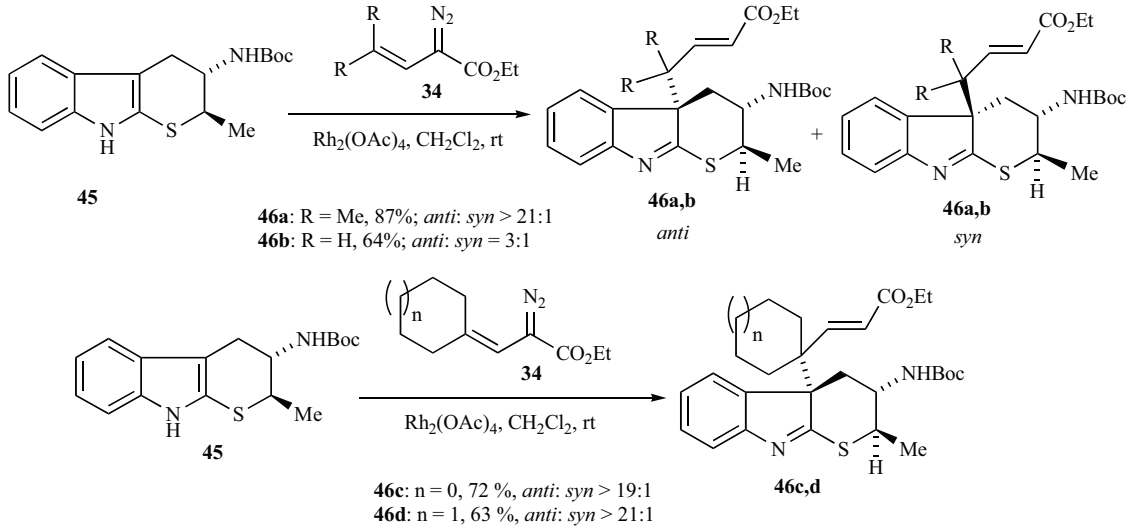
The diastereoselectivity further increased by substitution on aryl group *ortho* to the thioether. The ratio was increased to 11:1 with *ortho*-methyl thioether and to 15:1 with 2,6-dimethylphenyl thioether. The selectivity was maximum with *ortho*-isopropyl indole giving indoline **37** and **38** in 18:1 diasteroselectivity (entry 7,



Scheme 10. Diastereoselectivity in pyrroloindoline synthesis *via* thio-Claisen rearrangement.



Scheme 11. Spirocyclopentane synthesis.



Scheme 12. Quaternary substituted indolines from thiopyranylindole.

Table **3**). *Ortho*-methoxy and *ortho*-fluorophenyl thioethers resulted in lower selectivity which shows that the diastereoselectivity of this reaction is due to steric effect and perhaps, no electronic effect is operative here. These transformations led to the synthesis of structurally interesting substrates that would otherwise be difficult to prepare by using other methodologies.

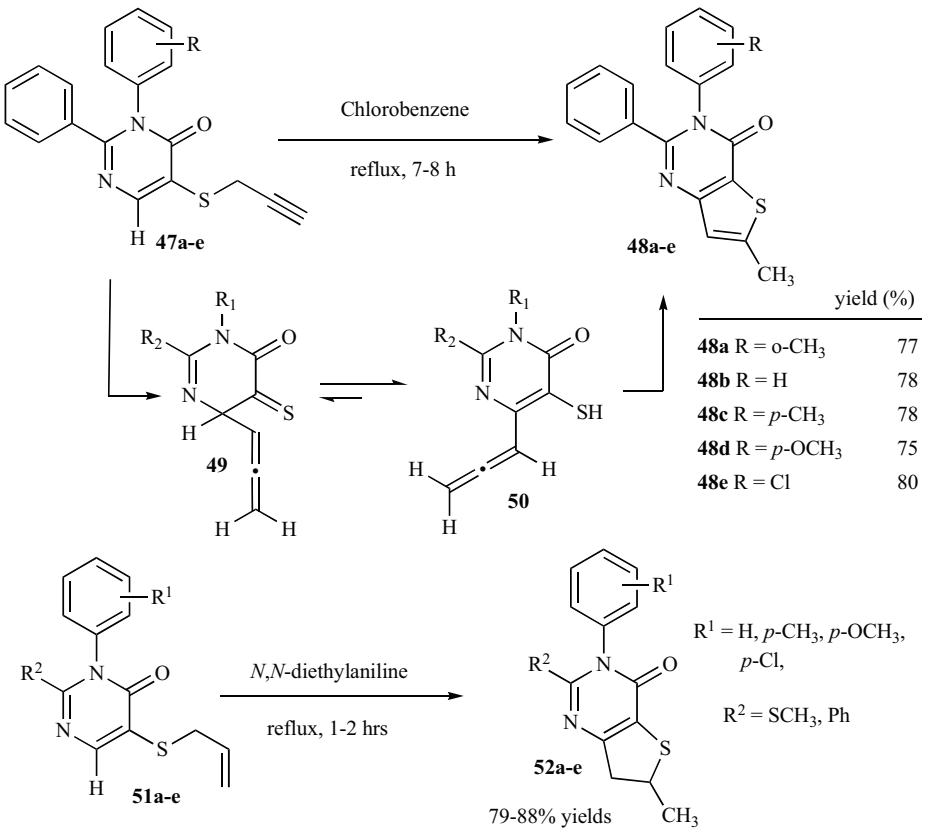
As the thio-Claisen rearrangement products are enriched with interesting functional groups, it would be possible to additionally derivatize these indolines. Thus, pyrroloindoline **41** was generated in 95 % yield from the acid-mediated cyclization of thioindoline **40** that was accessed from the reaction of **39** with **34a** in the presence of [Rh_2((*S*)-tbsp)$_4$] (Scheme **10**).

The treatment of substituted indoline **43**, having a quaternary C3 center, with a base resulted in a diastereoselective spirocyclization reaction to give **44** in 75% yield (Scheme **11**). The coupling/cyclization sequence outlined here represents a novel approach to halogenated spirocycles.

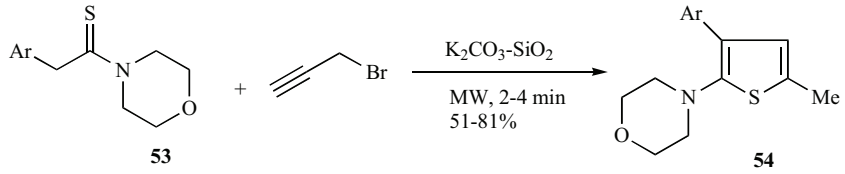
It was also observed that diastereoselectivity of the reaction was dependent upon the level of substitution on the diazo moiety; a *gem*-dimethyl-substituted vinyl carbenoid **34b** (R = Me) gave indoline **46a** having vicinal quaternary substitution in 87 % yield with a >21:1 diastereomeric ratio while the parent vinyl diazo-acetate **34c** gave much lower levels of diastereoselectivity. Both cyclohexenyl and cyclopentenyl diazo-acetates **34d** and **34e** gave the corresponding thioimidates **46c** and **46d**, respectively, with high *anti*/*syn* diastereoselectivity (Scheme **12**) [46].

4. SYNTHESIS OF SULFUR HETEROCYCLES

Pyrimidine and its derivatives have attracted the attention of an increasing number of synthetic organic chemists because of their reported broad range of biological activity and medicinal importance [47, 48]. Mahajan *et al*. developed a novel and regioselective approach towards the synthesis of five-membered fused thieno[3,2-*d*]pyrimidinones *via* a thermal thio-Claisen rearrangement. Pyrimidinones **47a-e** containing a propargyl unit at C_5-position is a potent auxiliary which on heating may undergo thio-Claisen rerrangement leading to the formation of variously substituted [5,6]-fused pyrimidinone derivatives **48a-e** [49]. The substrates **47a-e**



Scheme 13. Thieno[3,2-*d*]pyrimidin-4-one derivatives synthesis utilizing thio-Claisen rearrangement.



Scheme 14. Thio-Claisen rearrangement under microwave irradiation.

when treated in refluxing chlorobenzene, the thieno[3,2-*d*]pyrimidin-4-ones are obtained in 75-80 % yields *via* thio-Claisen rearrangement. The mechanistic pathway has been rationalized by initial [3,3] thio-Claisen rearrangement of the sulfides **47a-e** to form intermediate allenes **49** followed by enolisation to give enethiol **50**. The enethiol **50** can afford the thieno[3,2-*d*]pyrimidinone **48**, *via* the reported rearrangements [50]. The same group also examined the thermal transformation of pyrimidinones **51a-e** containing a allylic moiety at C5 position in chlorobenzene and also in high boiling solvent such as dichlorobenzene for several hours. But the substrates **51a-e** failed to give any rearranged product, unchanged starting material was recovered. Finally, the reaction was carried out in basic solvent *N*,*N*-DEA (b.p. 216 °C) for 1-2 h to afford the corresponding thio-Claisen rearrangement products **52a-e** in 79-80 % yields [51] (Scheme **13**).

A solvent free, solid-supported and microwave-assisted thio-Claisen rearrangement of *S*-propargylated thioamides **53** having an activated α-methylene group for the synthesis of tri-substituted thiophenes **54** has been developed by Moghaddam *et al*. [52] When a mixture of thioamides **53** and propargyl bromide were supported on anhydrous K_2CO_3 and silica-gel and irradiated in a microwave oven, a rapid and clean thio-Claisen rearrangement occurred to give tri-substituted thiophenes in moderate to good yields (51-81%) (Scheme **14**).

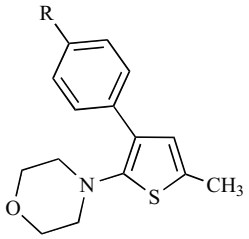
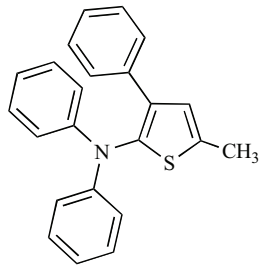
Several examples have been investigated and the results of the conventional thermal heating were compared with those of the microwave heating (Table **4**). It was seen that for the same yield in both methods, the use of microwave dielectric heating increases the relative rate of the reaction by 180 times.

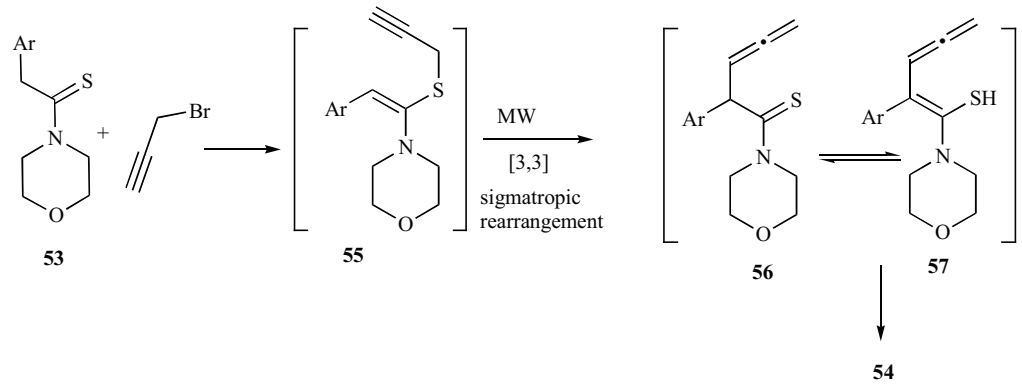
A mechanism proposed for this type of transformation is delineated in scheme **15**. Initially, the thioamide may undergo enolization, enhancing the nucleophilicity of the sulfur atom followed by *S*-propargylation to generate the intermediate **55**. Intermediate **55** may subsequently undergo a [3,3] sigmatropic rearrangement to yield the allene intermediate **56**, which is then converted into the intermediate **57** by tautomerization. Cyclization of this intermediate **57** finally leads to the formation of the thiophene ring.

This methodology could be used for the synthesis of sulfur containing triarylamines, which could be used as hole transport materials in electroluminescent display devices [53] and also as drug [54].

We have synthesized a number of hitherto unreported heterocyclic compounds derived from 4-hydroxydithiocoumarin [55, 56]. A series of 4-aryloxymethyl-7-chlorothiopyrano[2,3-*b*] thio-

Table 4. Comparative Study Between Heating and Microwave Reaction.

entry	Products		Δ		MW	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1		R = H	5	76	2	81
2		R = Me	5	70	2	75
3		R = Cl	6	50	3	54
4		R = Br	6	66	2	65
5		R = OMe	5	65	3	68
6		R = Ph	6	62	3	71
7		R = 2-naphthyl	6	53	3	51
8			6	61	4	70

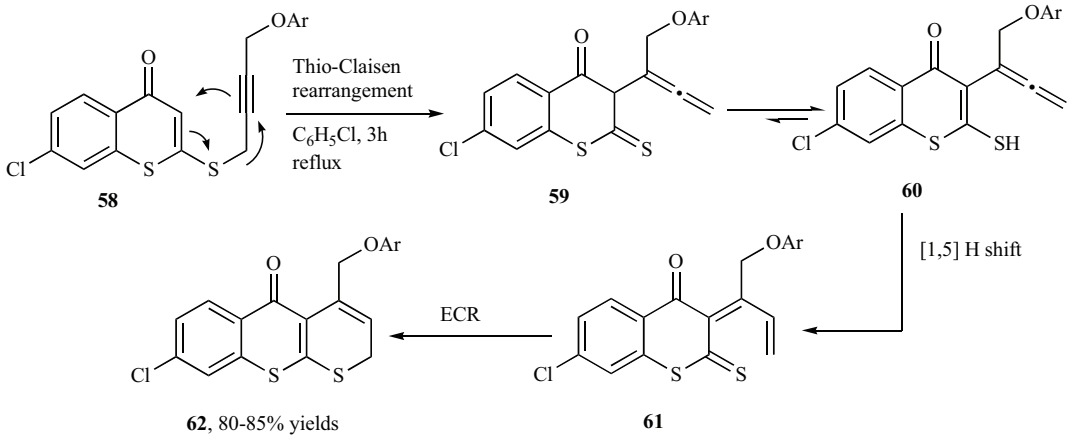


Scheme 15. Mechanistic overview of vinyl propargyl thio-Claisen rearrangement.

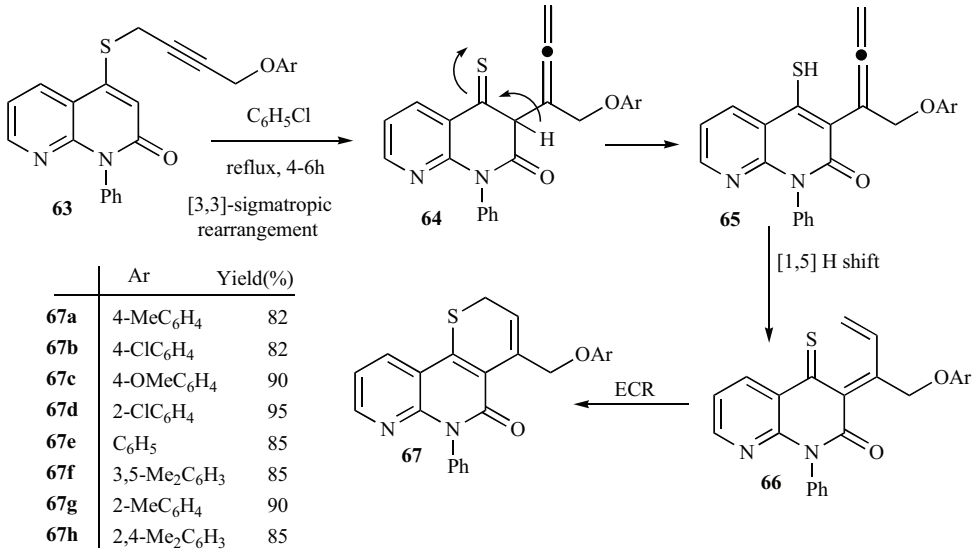
chromene-5(2H)-ones were synthesized [57] in 80-85% yields by the application of thio-Claisen rearrangement of 2-(4′-aryloxybut-2-ynylmercapto)thiochromen-4-ones in refluxing chlorobenzene for 3 h. The substrates 2-(4′-aryloxybut-2′-ynylmercapto)-7-chlorothiochromen-4-ones (**58**) were prepared in 80-82% yields by the phase transfer catalyzed alkylation of 7-chloro-4-hydroxydithiocoumarin [56] with a number of 1-aryloxy-4-chlorobut-2-ynes in the presence of BTEAC as the phase transfer catalyst [58] in 1 % aq. NaOH-$CHCl_3$ for 5 h. The substrates **58** contain the but-2-ynylthioenone moiety as well as the arylprop-2-ynyl ether moiety and thus offer scope for two different possibilities of [3,3] sigmatropic rearrangement. The aliphatic Claisen rearrangement requires lower activation energy than that of the aromatic counterpart. The aromatic sextet is disturbed in the transition state of the aromatic counter part. Therefore, substrate **58** when heated in chlorobenzene gave the corresponding thio-Claisen rearrangement products **62**. The formation of products **62** from the substrate **58** may be easily explained by an initial [3,3] sigmatropic rearrangement followed by rapid enolization to give the intermediate allenyl thiol **60**, [1,5] hydrogen shift followed by a 6π-electrocyclic ring closure to finally give the products **57** (Scheme **16**).

1,8-Naphthyridinones and their derivatives have attracted considerable attention primarily because the 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances and exhibited various medicinal and biological activities [59, 60]. 4-Hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one and its derivatives have been used as inhibitors of sulfidopeptide leukotrienes, the major component of SRS-A release [61]. Majumdar *et al*. utilized thio- and oxy-Claisen rearrangements for the synthesis of azanaphthyridine derivatives **67** efficiently starting from 4-(4′-aryloxybut-2-ynylthio)-1-phenyl-1,8-naphthyridin-2(1*H*)-ones **63**. The formation of the products **67** from the substrates **63** may be rationalised by the occurrence of similar events as stated in the previous case (Scheme **17**) [62]. Compounds **62** on further treatment with $AlCl_3$ in dry dichloromethane at rt afforded desired polyheterocyclic products.

We have also exploited the thio-Claisen rearrangement for synthesizing pyrone-annulated sulfur heterocycles [63, 64]. In recent years, increasing efforts have been given to the synthesis of pyran-2-one derivatives due to their diverse pharmacological properties [65] and these compounds are widely present in naturally occurring physiologically active substances in the form of isolated and fused



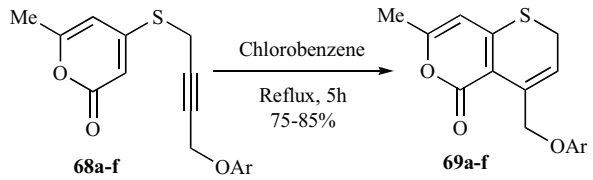
Scheme 16. Thio-Claisen rearrangement of 2-(4′-aryloxybut-2′-ynyl-mercapto)thiochromen-4-ones.



	Ar	Yield(%)
67a	4-MeC_6H_4	82
67b	4-ClC_6H_4	82
67c	4-$OMeC_6H_4$	90
67d	2-ClC_6H_4	95
67e	C_6H_5	85
67f	3,5-$Me_2C_6H_3$	85
67g	2-MeC_6H_4	90
67h	2,4-$Me_2C_6H_3$	85

Scheme 17. Vinyl-propargyl thio-Claisen rearrangement to give azanaphthyridine derivatives.

ring systems [66]. The substrates 4-(4′-aryloxybut-2-ynylthio)-6-methylpyran-2(1H)-ones (**68a-f**) were subjected to refluxing in chlorobenzene for 5h to afford the corresponding thio-Claisen rearrangement products **69a-f** in 75-85% yields. Between the two possibilities of Claisen rearrangements, the compounds **68** readily undergo thio-Claisen rearrangement and ring closure to give the cyclized products **69** (Scheme **18**).



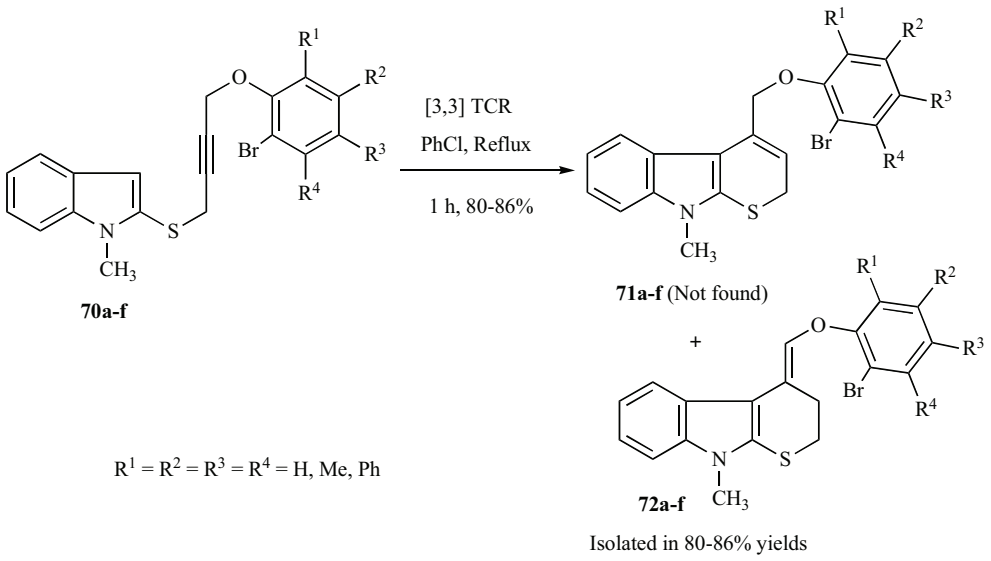
	Ar	yields (%)
69a	2-BrC_6H_4	80
69b	2-Br-3-MeC_6H_3	82
69c	2-Br-4-$OMeC_6H_3$	75
69d	1-Br-2-$C_{10}H_6$	85
69e	2-Br-4-MeC_6H_3	75
69f	2-Br-4,6-$Me_2C_6H_2$	80

Scheme 18. Synthesis of of thiopyrano[3,2-*c*]pyran-5-one derivatives.

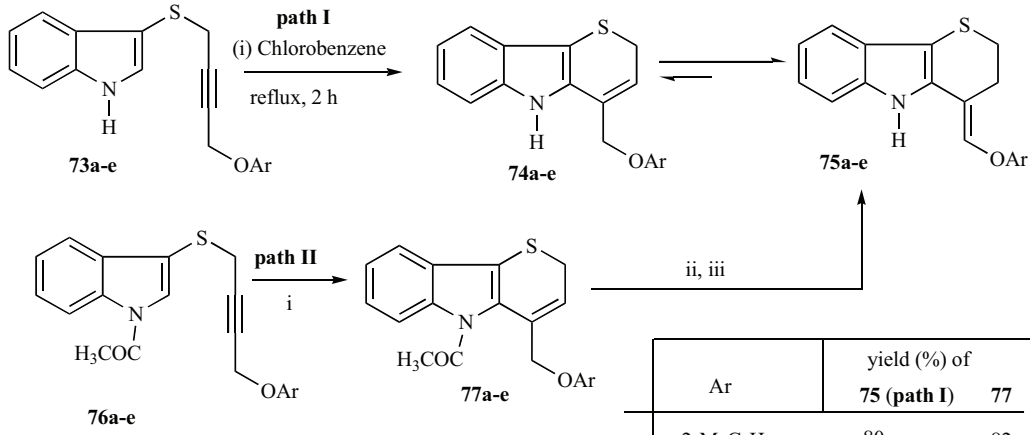
We have extended the thio-Claisen rearrangement to the substrates **70** possessing the but-2-ynylindole-2-yl sulfide moiety as well as the aryl but-2-ynyl ether moiety. The thio-Claisen rearrangement [57, 67] in the sulfide moiety may require relatively lower activation energy perhaps due to the lower aromaticity of the pyrrole ring of the indole nucleus. As a consequence, sulfides **70a-f** on refluxing in chlorobenzene (132 ^{o}C) for 1h afforded the thio-Claisen rearrangement products **72a-f** in 80-86% yields. Here it is interesting to note that the thio-Claisen rearrangement products of the indole system are *exocyclic* where as the coumarin and quinolone systems produce *endocyclic* [57, 62] products (Scheme **19**) [68].

Formation of the endocyclic intermediates **71**(not isolated) from the substrates **70** may be explained [69] by a similar mechanism as stated earlier. The endocyclic intermediates 4-aryloxymethyl-9-methyl-2,9-dihydropyrano[2,3-*b*]indoles (**71**) may subsequently undergo tautomerization to give the exocyclic double bonded [70] products **72**.

Stereoselectivity in the thio-Claisen rearrangement products was observed when the substrates 3-(4′-aryloxybut-2′-ynylthio)-indoles **73a-e** and the corresponding *N*-acetylated analogues **76** were refluxed in chlorobenzene. Thio-indole derivatives **73a-e** gave the *exocyclic* double bonded product **75a-e** in excellent yields of 78-84 % *via* the intermediates **74**. Whereas the *N*-acetylated analogues **76a-e** gave the *endocyclic* double bonded product **77a-e** in 77-82% (Scheme **20**) [71].



Scheme 19. Thio-Claisen rearrangement of 2-(4′-aryloxybut-2′-ynylthio)-1-methylindoles.



	Ar	yield (%) of 75 (path I)	77
a	2-MeC_6H_4	80	82
b	4-$MeOC_6H_4$	84	82
c	4-MeC_6H_4	83	81
d	2,4-$Me_2C_6H_3$	78	79
e	2,3-$Me_2C_6H_4$	79	77

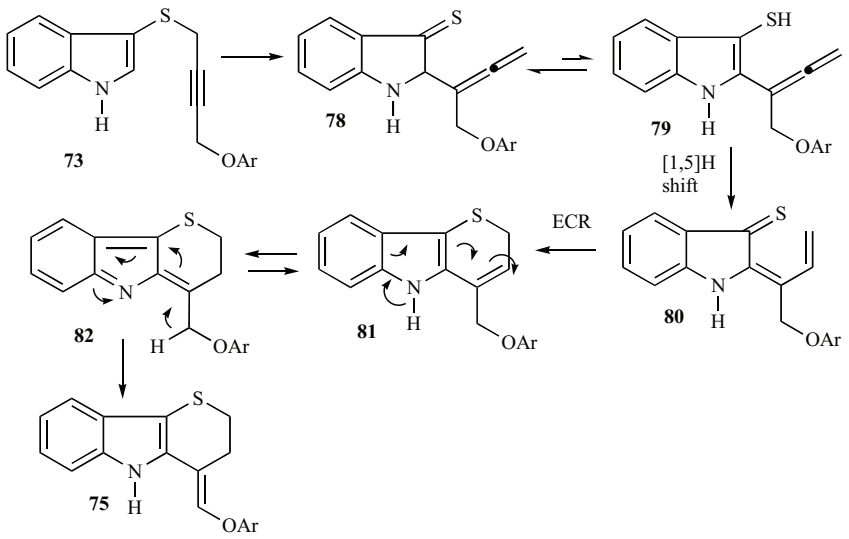
Scheme 20. *Reagents and conditions:* (i) Chlorobenzene, reflux, 2 h; (ii) CH_3ONa (1.5 equiv), CH_3OH, -15 °C, stirring, 1.5 h. (iii) Chlorobenzene, reflux, 1 h.

The results were easily explained by the thermal isomerization of **73a-e** to **74a-e**. The thio-Claisen rearrangement of precursors **73**, gives the *endocyclic* double bonded products **74a-e** that was followed by further thermal isomerization to give products **75a-e**. But in the presence of electron withdrawing acetyl group at the indole nitrogen (**76**), the thermal isomerization is inhibited and hence the *endocyclic* double bonded products were isolated (Scheme **21**). However, these could be easily transformed to **75a-e** by deprotection followed isomerization.

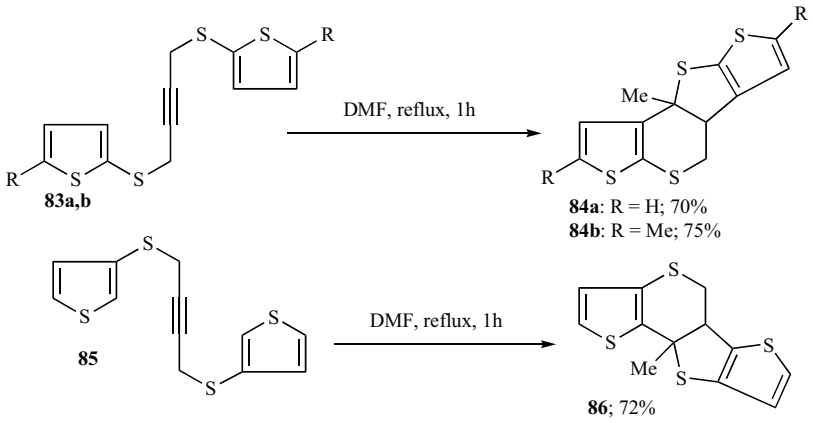
For the first time we have successfully performed the sequential thio-Claisen rearrangement of 1,4-bis(2-thienylsulphanyl)but-2-ynes (**83a,b)** for the construction of [6, 5] fused heterocycles. The starting materials **83a,b** were prepared by the reaction of 2-mercaptothiophene with 1,4-dichlorobut-2-yne in dry ether under inert atmosphere at room temperature [72]. Compounds **83a,b** contain 2-vinyl propargyl sulphide moiety and are very prone to undergo tandem Claisen rearrangement in refluxing DMF to afford the tetracyclic sulphur compounds **84a,b** (Scheme **22**) [72].

The formation of the intermediates **90a,b** (not isolated) from the substrates **83a,b** can be rationalized by the occurrence of similar sequence of events as previously described. The newly formed intermediates still possess an allyl thienyl sulphide moiety and readily undergo a further [3,3] sigmatropic rearrangement and enolization to give **91**. Finally, a 5-*exo-trig* cyclization of **91** may give **84** (Scheme **23**). This methodology displayed appreciable regioselectivity and is attractive by its simplicity. This methodology may prove useful in this type of synthesis.

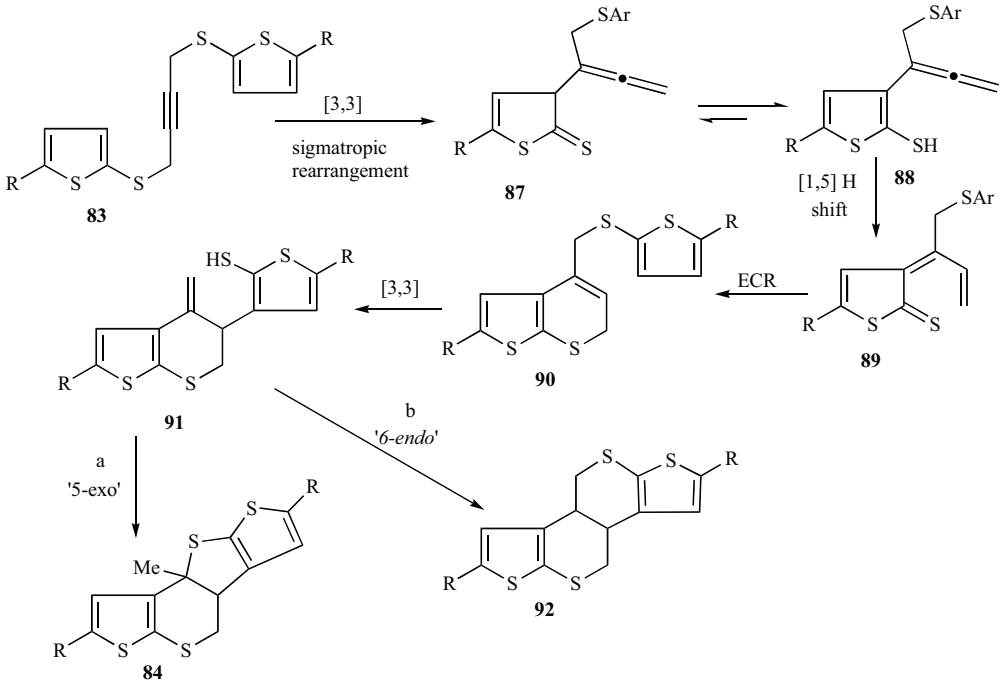
Our group recently reported [73] the Claisen rearrangement of 4-(4′-aryloxybut-2-ynylthio)thiocoumarins **93**, where also there is a scope for two different Claisen rearrangements [57, 62, 63, 67, 68]. The substrates **93** possessing two potential sites for [3,3] sigmatropic rearrangement: an aryl propargyl ether moiety and a vinyl propargyl sulfide moiety. All the substrates **93** underwent [3,3] sigmatropic rearrangement at the vinyl propargyl sulfide moiety when heated at reflux in chlorobenzene to give thiopyrano[3,2-*c*]thiochromen-5-one **94** in good yields (78-92%) (Scheme **24**). As



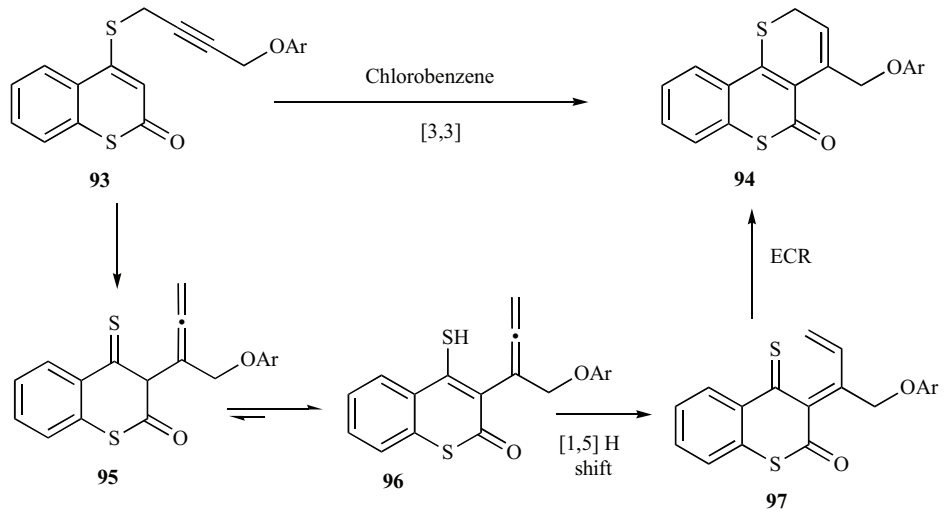
Scheme 21. Plausible mechanism of the thio-Claisen rearrangement.



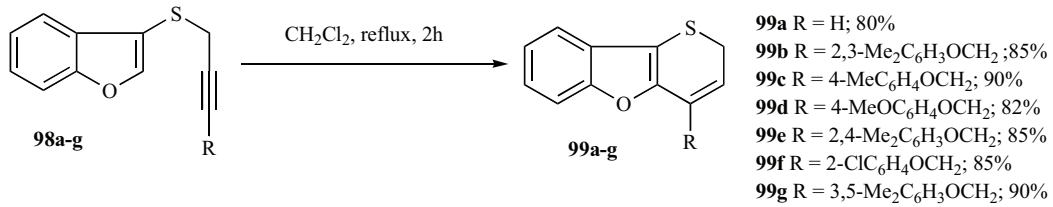
Scheme 22. Synthesis of sulfur tetracycles *via* tandem thio-Claisen rearrangement.

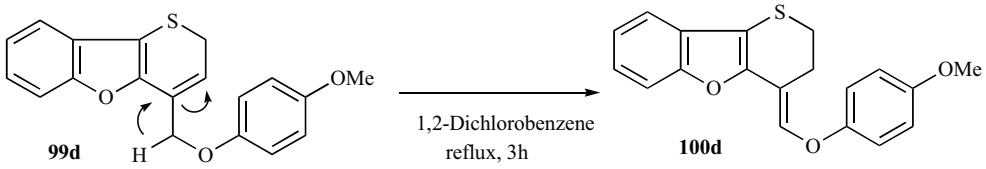


Scheme 23. Mechanistic path of double thio-Claisen rearrangement.



Scheme 24. Predominance of vinyl-propargyl rearrangement over aryl propargyl one.





Scheme 25. Thio-Claisen rearrangement of *S*-propargyl thiobenzofuran derivative.

the products **94** possess the aryl allyl ether segment, it was then allowed to reflux in 1,2-DCB in the presence of *N*,*N*-DEA for 10-12h to give the phenolic products. The oxy-Claisen step was best catalyzed by anhydrous $AlCl_3$ in dry CH_2Cl_2 within just 0.5-1 h.

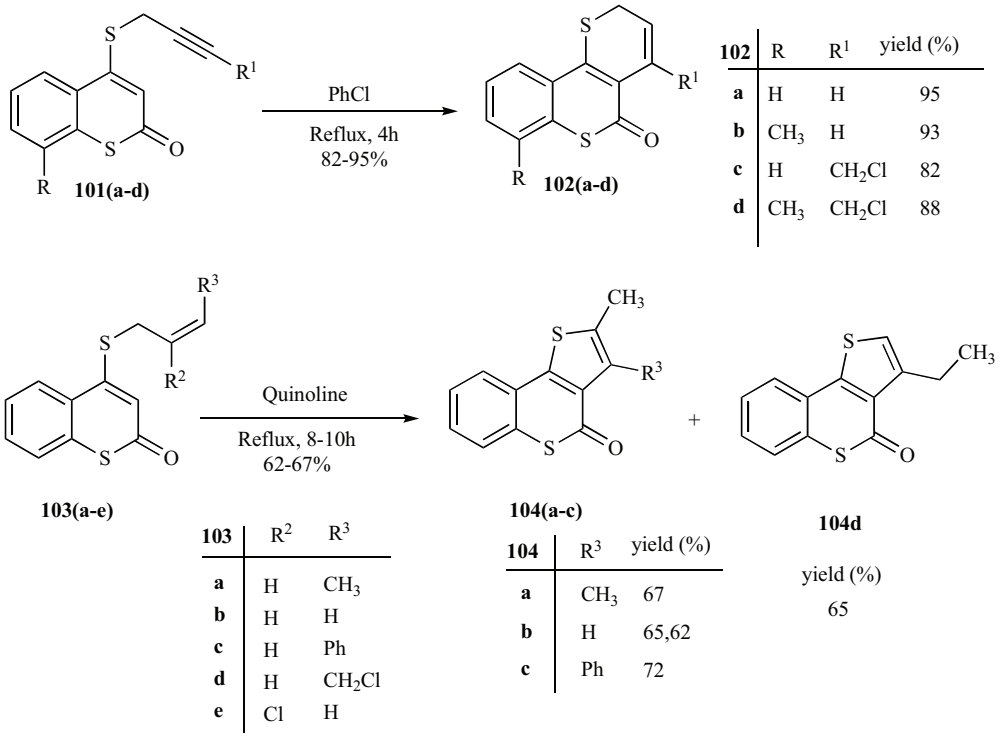
Other examples of the thio-Claisen rearrangement were observed when substrates 3-(4′-aryloxybut-2-ynylthio)benzofuran (**98a-g**) were refluxed in dichloromethane (Scheme **25**) [74]. The cyclized products 2*H*-benzo[*b*]thiopyrano[2,3-*d*]furans (**99a-g**) were obtained in 80-90 % yields. The starting precursors **98a-g** are very unstable and undergo thio-Claisen rearrangement when kept at room temperature although at a slower rate. For complete conversion, the substrates were refluxed in dichloromethane (bp 39 ^oC) and the reaction was monitored by TLC. Complete conversion was achieved in 2h to afford the cyclic products. The products **99b-g**, containing additional allyl aryl ether system were subjected to a second Claisen rearrangement. However, this would require higher temperature than the first [3,3] sigmatropic rearrangement to disturb the aromatic sextet of the aryl part. At higher temperature in refluxing 1,2-dichlorobenzene, (b.p. 180 ^oC) **99d** underwent [1,3] hydrogen shift and the endocyclic double bond of compound **99d** was transformed to an exocyclic double bond, giving product **100d** without any formation of [3,3] Claisen product. Repetition of the reaction with the corresponding thio analogue was also unsuccessful.

We have also reported [75] the formation of various fused thiocoumarin-annulated thiopyran and thiophene ring systems by the application of thio-Claisen rearrangement. For this purpose, the starting materials **101** and **103** were synthesized by the usual PTC conditions. When the substrates **101** were subjected to heating in refluxing chlorobenzene for 4 h, the six-membered thiopyran ring fused thiocoumarins **102a-d** were isolated in 82-95% yields. Generally, the thio-Claisen rearrangement of propargylic systems occurs under mild reaction condition as compared to the allylic precursors [75, 76] **103a-d** and consequently we have carried out the Claisen rearrangement of the substrates **101** in a low boiling solvent. The thio-Claisen rearrangement of **103** was carried out in a higher boiling and basic solvent such as quinoline for a smooth reaction to give the corresponding products **104** in good yields (62-72%) (Scheme **26**).

The formation of different products **104**, from the corresponding allyl sulfides **103** may be explained by [3,3] sigmatropic rearrangement, followed by rapid enolization to form the intermediate ene-thiol **106**. Base (quinoline) catalyzed cyclization then afforded **104a-c** from **103a-c** (Scheme **27**).

Consequntly intermediate **107** corresponding to one obtained from **103d** can be written as an equivalent structure of **106d** by the single bond rotation and base-catalyzed cyclization, which may then give the product **104d** by two consecutive 1,3-prototropic shift.

The thieno[2,3-*b*]thiochromen-4-ones are found to form the core structures of many important drugs used for the treatment of psychotic disturbances. We have disclosed [77] a short route for the synthesis of this intermediate compounds by the implementation of the thio-Claisen rearrangement. For this investigation, the precursors **115a-d** were prepared in 60-85% yields by phase transfer catalyzed alkylation of 7-chloro-4-hydroxydithiocoumarin **113** with



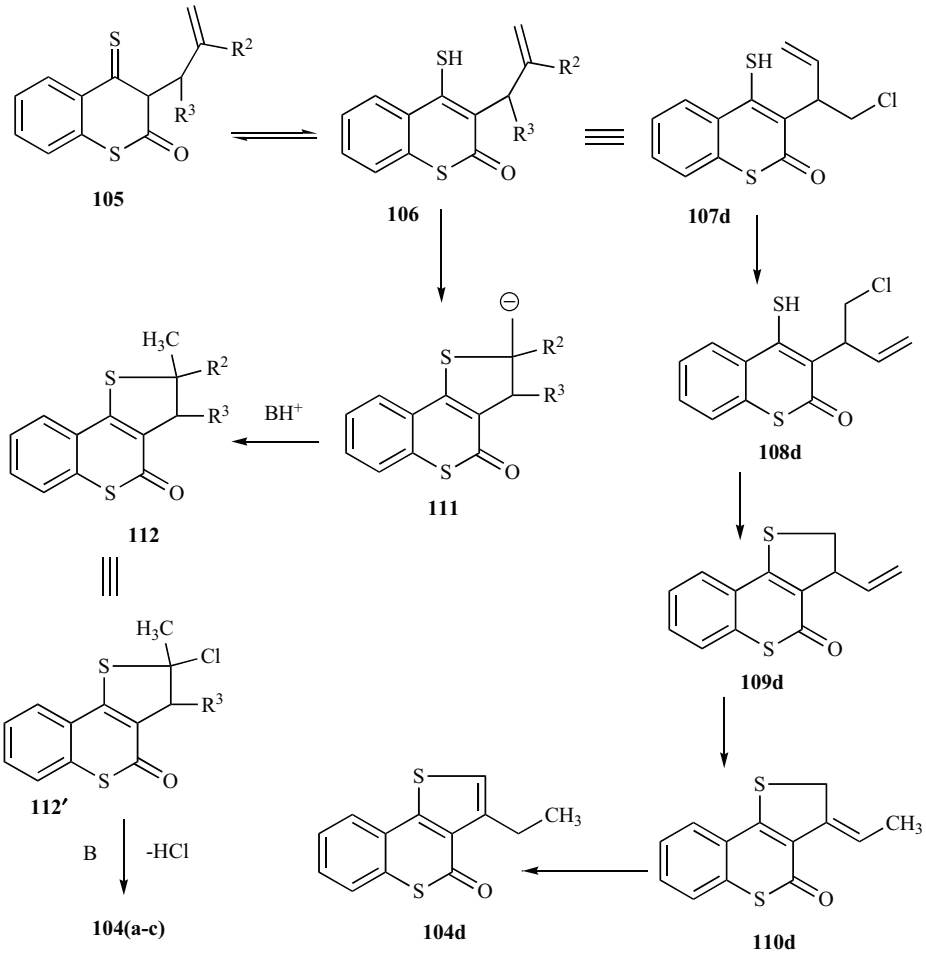
102	R	R^1	yield (%)
a	H	H	95
b	CH_3	H	93
c	H	CH_2Cl	82
d	CH_3	CH_2Cl	88

103	R^2	R^3
a	H	CH_3
b	H	H
c	H	Ph
d	H	CH_2Cl
e	Cl	H

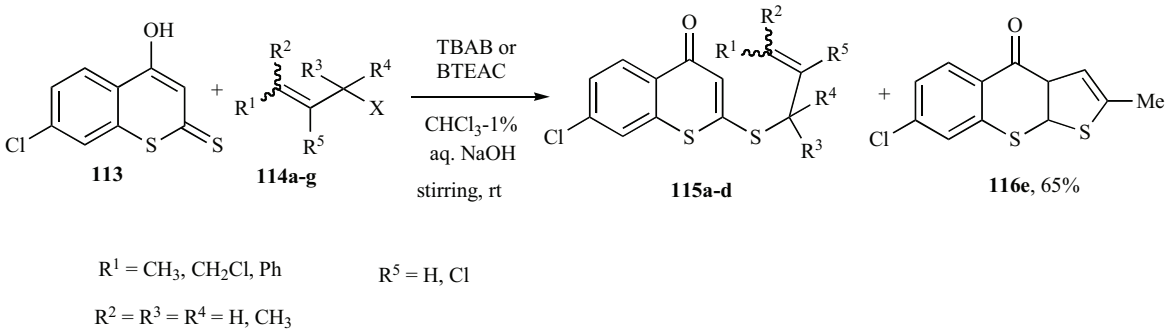
104	R^3	yield (%)
a	CH_3	67
b	H	65,62
c	Ph	72

yield (%)
65

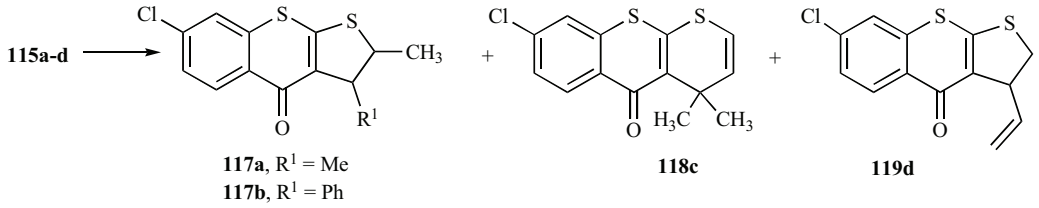
Scheme 26. Comparative study of propargyl and allyl thio-Claisen rearrangement.



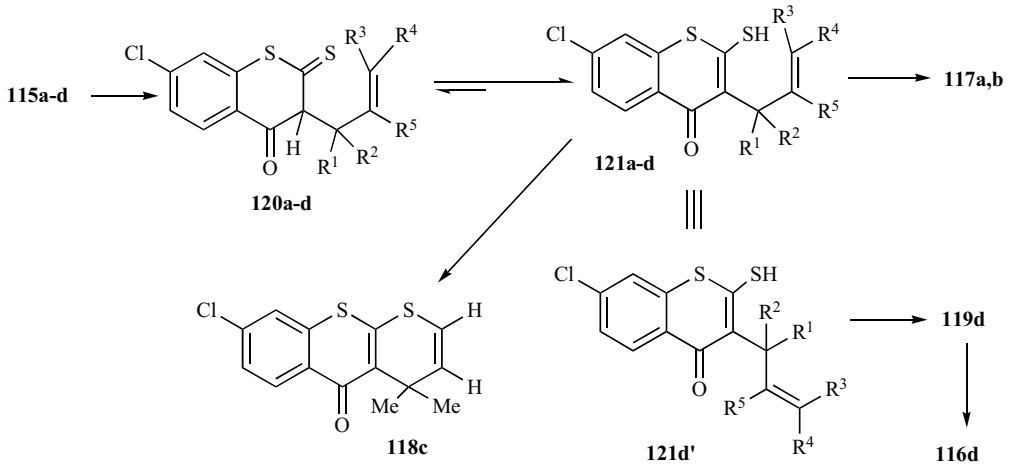
Scheme 27. Plausible mechanistic explanation of the rearrangement.



Scheme 28. Synthesis of thio-Claisen precursors.



Scheme 29. Formation of a varity of cyclized products *via* thio-Claisen rearrangement.



Scheme 30. The plausible reaction path.

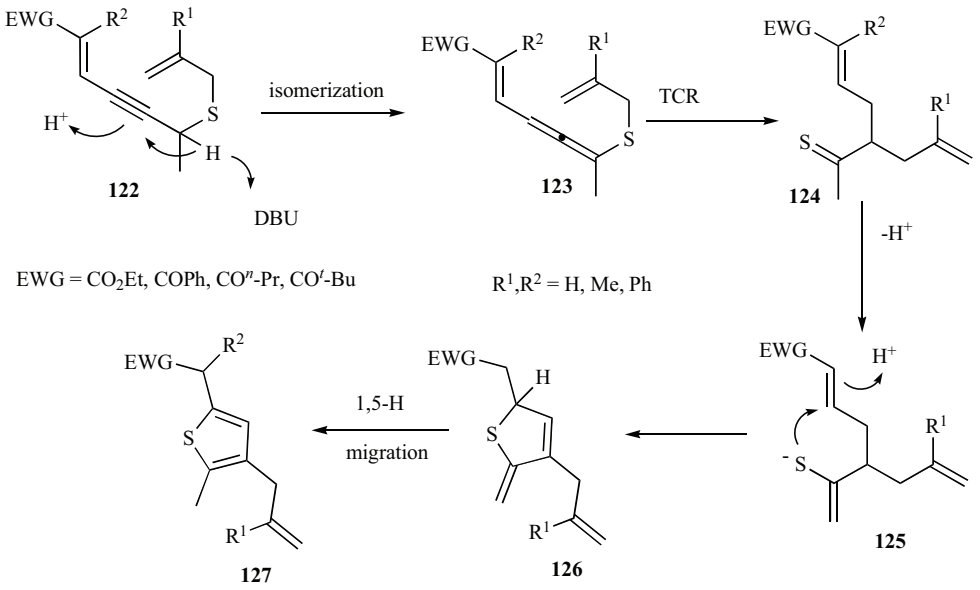
different allyl halides **114a-f** in the presence of a catalytic amount of TBAB or (BTEAC) in chloroform-aqueous sodium hydroxide (1%) at room temperature for 5h. Pleasingly, during the course of the phase transfer catalyzed alkylation substrates **114g** and **113** underwent direct cyclization reaction to give the five-membered cyclized product 2-methylthieno[2,3-*b*]-4*H*-thiochromen-4-one **111e** in 65% yield (Scheme **28**).

On the other hand, when the thio-Claisen rearrangement of **115a-d** were carried out in chlorobenzene [50] and *N*,*N*-DEA [78], no appreciable change was observed. However, when the reaction was carried out in quinoline (bp 238 °C) with **115a**, a new product **117a** was obtained in 80% yield. Similarly, **115b** gave the corresponding rearrangement product **117b** in 70% yield. Interestingly, substrates **115c** and **115d** gave two different types of products such as **118c** and **119d** respectively (Scheme **29**).

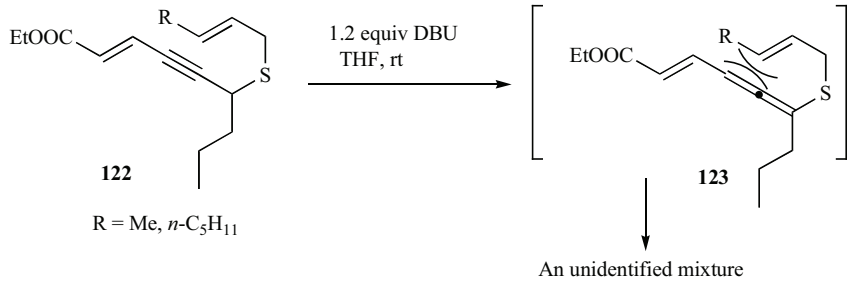
The formation of the products **117a,b** and **118c** may be rationalized similarly as described earlier in the case of the products **104**. Product **119d** was obtained from **121d'** that may form **116d** by two sequential [1,3] prototropic shift (Scheme **30**).

Sulfur-assisted isomerization of propargyl-allenyl system has been an useful and efficient method to the library of thio-allenes [79, 80]. The allene moiety generally enhances the diversity of the reaction possibility compared to that of a normal olefin. It is hypothesized that the allenyl allyl sulfides should undergo thio-Claisen rearrangement more smoothly than allyl vinyl sulfides [7, 81], giving allyl-enethiones as the intermediates. Zhou *et al*. reported [82] a sulfur-assisted five-cascade sequential reaction, wherein the *in situ*-generated allenyl allyl sulfides **123** underwent thio-Claisen rearrangement, leading to 2-allyl-2-enethiones **124**. This rearrangement was followed by a thione enolization, an intramolecular Michael addition, and 1,5-proton migration/ aromatization to give allyl thiophenes **127** as the final products (Scheme **31**).

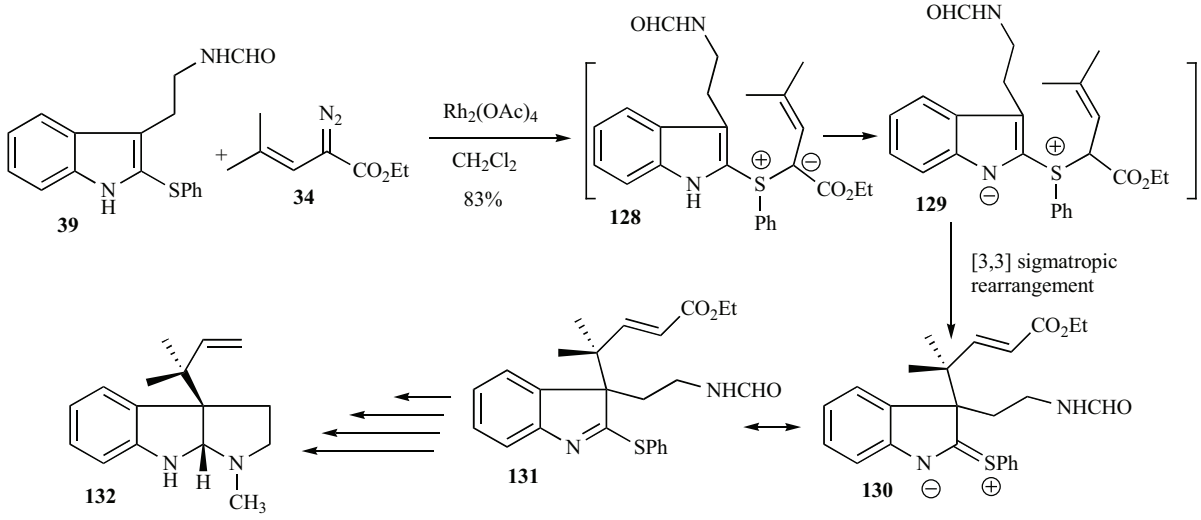
The optimized condition for this reaction is 1.2 equiv. DBU in THF at room temperature. It is notable that a substituent at C3 of the allyl group prevents the reaction, probably because the transition state of the key step (TCR) is sensitive to steric hindrance (Scheme **32**). The substituent at the C1 of the *S*-propargyl group must have a α-proton which allows the enolization of the intermediate enethione to enethiol. Thus, starting materials with no substituent, or *tert*-butyl and phenyl group at C1 cannot give the expected products.



Scheme 31. Thio-Claisen rearrangement of allenyl allyl sulfides.



Scheme 32. The influence of substitution at C3 of the allyl group.

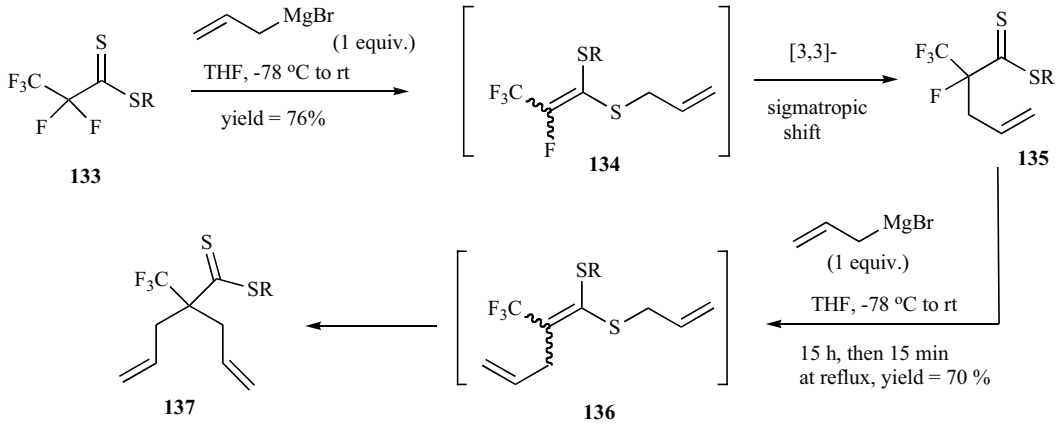


Scheme 33. Synthesis of the debrominated analog of dihydroflustramine C utilizing thio-Claisen rearrangement.

5. APPLICATION IN NATURAL PRODUCTS SYNTHESIS

Rainier and co-workers have efficiently synthesized highly functionalized pyrroloindoline ring systems present in a variety of natural and non-natural products [83]. The synthesis of the debrominated analogue of dihydroflustramine C utilizing the scope and limitations of the sulfur ylide initiated thio-Claisen rearrangement has been reported (Scheme **33**) [84]. Rainier *et al*. observed that C(3) quaternary substituted indolines **131** can be generated from the coupling of 2-thioindoles **39** with vinyl diazoacetates **34** in the presence of Rh(II) catalysts [44-46]. It has been proposed that **131** results from a [3,3]-sigmatropic rearrangement of the charge separated ion pair **129** obtained from the sulfur ylide **128** by a subsequent proton transfer [85, 86].

Finally, debrominated analog of dihydroflustramine C (**132**) was synthesized from **131** in six steps. This synthetic protocol may be useful for the synthesis of indoline containing natural products [87, 88].



133 **134** **135** **136** **137**

Scheme 34. Synthesis of various symmetrical or nonsymmetrical α-trifluoromethyl α-bis(unsaturated) dithioesters.

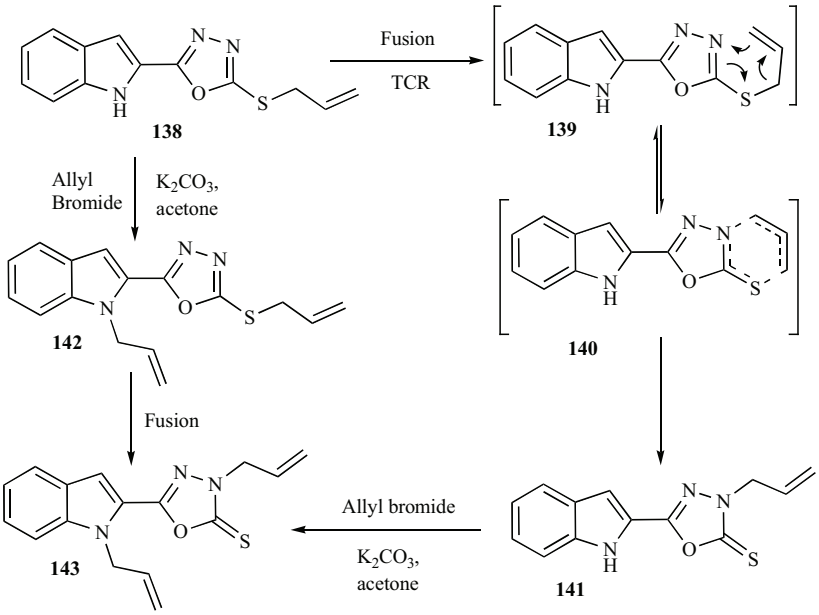
Table 5. Reaction of *S*-butyl Pentafluorodithioesters with Allylic Grignard Reagents

entry	starting	Grignard regt. in step (I)	mono-substituted product (%)	Grignard regt. in step (II)	di-substituted product (%)
1	**133a**	MgCl	**135a** 76%, 83%	MgBr 15 min.	**137a**, 68%
2	**133a**	MgCl		MgCl 45 min.	**137b**, 51%
3	**133a**	MgCl	**135b**, 83%	MgBr 1 h 30 min.	**137c**, 65%
4	**133b**	BnMgBr	**135c**, 85%	MgBr 15 min.	**137d**, 75%
				MgCl 1 h	**137e**, 88%

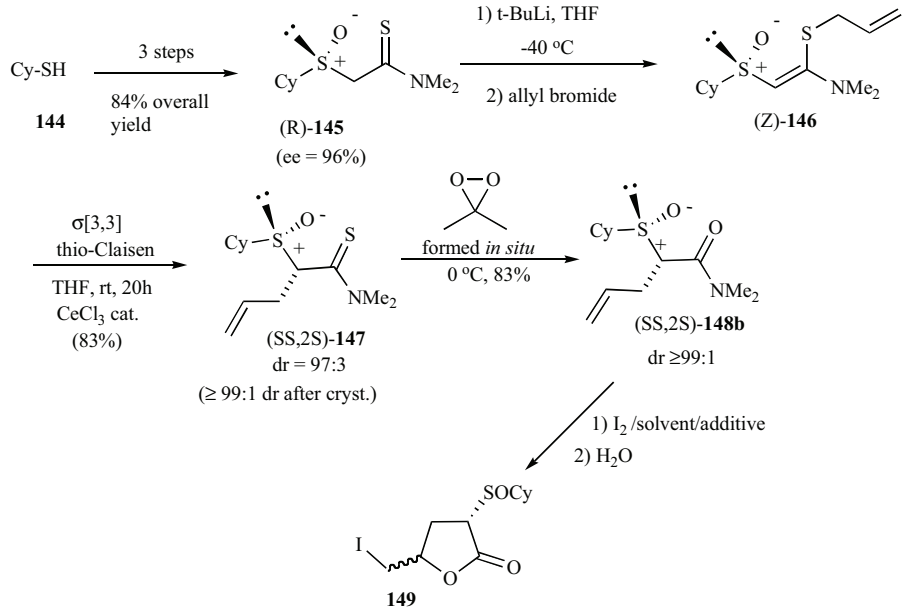
6. MISCELLANEOUS

Portella *et al*. [89] have described that the domino reaction, thiophilic addition of an organomagnesium reagent, *β*-elimination of fluoride and [3,3]-sigmatropic rearrangement are a versatile approach for the synthesis of various unsaturated fluorinated dithioesters. *n*-Butyl pentafluorodithiopropanoate **133a** was reacted with an allyl Grignard reagent to evaluate the relevance of the proposed approach. It was observed that the reaction led directly to α-fluoro α-trifluoromethyl α-allyl dithioester **135a-c** in 76-90 % isolated yields after purification on a pad of silica gel (eluent: pentane) (Scheme **33**). The first two steps e.g. thiophilic nucleophilic allylation and fluoride elimination gave the intermediate ketene dithioacetal **134**. Dithioester **135** was further treated with 1 equiv of allylmagnesium bromide according to the previous conditions. Despite fast formation of the intermediate *S*-allyl ketene dithioacetal **136** [90], the second rearrangement was slower due to the bulky trifluoromethyl and allyl groups present on the vinylic carbon [91]. Complete conversion of **136** into **137** was achieved after 3 days at room temperature or within 15 min under reflux.

To test the generality of the reaction various dithioesters **135a-c** were then treated with allylic Grignard reagents (Table **5**). The progress of each reaction was monitored by ^{19}F NMR after 15 h of



Scheme 35. Thio-aza-Claisen rearrangement of *S*-allyl and *S,N*-bisallyloxadiazole.



Scheme 36. Thio-Claisen transposition.

stirring and the reaction mixture was then heated at reflux until complete conversion of the intermediate *S*-allyl ketene dithioacetals of the type **136** into the corresponding dithioesters **137a-e**.

A thio-aza-Claisen rearrangement was detected when the allylthioether **138** was fused under atmospheric conditions to give the rearranged product **141** in excellent yield within just 5 minutes. The allyl group migrates from sulfur to the *ortho* nitrogen functionality. Similarly, *S*,*N*-bis-allyl precursor **142** gave the *N*,*N*-bis-allyl product **143** in high yield. Thermal intramolecular [3,3]-sigmatropic reorganization of the allyl group from sulfur to nitrogen may take place *via* a six-membered cyclic transition state **140**, in a concerted six electron reorganization, and accompanied by rearomatization yielding the *N*-allyl derivative **141** (Scheme **35**) [92]. The rearrangement was strongly supported by the appearance of a ^{13}C NMR signal for C=S bond at δc 175 ppm. The migration of the corresponding S-benzyl group in the *S*,*N*-bis-benzyl derivative by fusion was unsuccessful. This proved the rearrangement to be a regular [3,3]-sigmatropic change rather than a non-thio-Claisen type migration of the allyl moiety *via* a free radical mechanism.

7. CATALYZED THIO-CLAISEN REARRANGEMENT

Alike other Claisen rearrangements e.g. oxy- and amino-Claisen rearrangements, thio-Claisen rearrangement is also facilitated by the use of a catalyst. This effect is much less documented than that of the other rearrangements. Only a few examples are available in the literature [15, 93].

Metzner *et al*. [94] disclosed an efficient asymmetric synthesis of α-sulfinyl *γ*-unsaturated amide **148b** (or its enantiomer) from cyclohexyl thiol and a very cheap chiral auxiliary: diacetone-D-glucose [28b] in five steps and in 40% overall yield. The asymmetric thio-Claisen rearrangement of the (*Z*)-ketene aminothioacetal **146** was directed by the cyclohexylsulfinyl group with both absolute and relative stereocontrol. The thio-Claisen precursor **146** was prepared by deprotonation of (*R*)-**145** with *t*-BuLi and subsequent

allylation at the sulfur atom by allyl bromide. The rearrangement of the compound **146** into (*SS*,2*S*)-**147** was improved using $CeCl_3$ as a catalyst at room temperature giving an excellent diastereomeric ratio of 97:3 (99:1 after recrystallization), an enantiomeric excess of 96%, and 83% yield. Finally, oxidation of the thioamide **147** with an oxidizing agent, dimethyldioxirane [95], generated *in situ* from oxone, acetone, and $NaHCO_3$ followed by iodolactonization, the target product **149** was isolated in yield (Scheme **36**).

CONCLUSION

This brief review covers only the recently published examples of the thio-Claisen rearrangement in various synthetic strategies. In most cases, only the thio-Claisen rearrangement step has been described. Unfortunately, relatively much less efforts/activity has been devoted to this area compared to its counterparts viz., the oxy-Claisen and aza-Claisen rearrangements. There is still scope for further work and development in this area. We hope this brief review will encourage researchers to take up new challenges for the synthesis of complex natural products and other useful materials by the application of thio-Claisen rearrangement.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

TCR	=	Thio-Claisen Rearrangement
DFT	=	Discrete Fourier Transform
NICS	=	Nucleus-Independent Chemical Shift
NBO	=	Natural Bond Orbital
HOMO	=	Highest Occupied Molecular Orbital
LUMO	=	Lowest Unoccupied Molecular Orbital
mCPBA	=	Meta Chloro Perbenzoic Acid
DIC	=	Diisopropylcarbodiimide
HOAt	=	7-Aza-1-hydroxybenzotriazole
LDA	=	Lithium Diisopropylamide
THF	=	Tetrahydrofuran
N,N-DEA	=	N,N-Diethyl acetamide
BTEAC	=	N-Benzyl-N,N,N-Triethylammonium Bromide
TBAB	=	Tetrabutylammonium Bromide
DMF	=	Dimethylformamide
DCB	=	Dichlorobenzene
TLC	=	Thin Layer Chromatography
PTC	=	Phase Transfer Catalysis
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene

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