Recent synthesis of thietanes

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Abstract
Thietanes are important aliphatic four-membered thiaheterocycles that are found in the pharmaceutical core and structural motifs of some biological compounds. They are also useful intermediates in organic synthesis. Various synthetic methods of thietanes have been developed, including inter- and intramolecular nucleophilic thioetherifications, photochemical [2 + 2] cycloadditions, ring expansions and contractions, nucleophilic cyclizations, and some miscellaneous methods. The recently developed methods provide some new strategies for the efficient preparation of thietanes and their derivatives. This review focuses on the synthetic methods to construct thietane backbones developed during 1966 to 2019.

Review

1. Introduction
Thietanes are a class of important aliphatic four-membered thiaheterocycles. Some simple alkyl and dialkyl thietanes are components of anal gland secretions of the stoat [1] and the ferret [2]. Some pharmaceutical and biological thietane-containing compounds include thiaanalogue thietanose nucleosides 1 and 2 [3,4], and the spiroannulated glyco-thietane nucleoside 3 [5] of the antiviral (anti-HIV and HSV) drug oxetanocin A, the D-ring-modified thia derivatives 4 and 5 of the anticancer drug taxoids and docetaxels [6], thiathromboxane A2 6 [7], pesticide 7 [8], and the sweetener 8 [9] (Figure 1). Thietanes also serve as important and useful intermediates and versatile building blocks in organic synthesis for the preparation of sulfur-containing acyclic and heterocyclic compounds [10,11]. Several synthetic methods for thietanes have been developed and reviewed [12-14]. One traditional route is the intermolecular double substitution (cyclic thioetherification) of 1,3-dihaloalkanes, sulfonates of 3-haloalkan-1-ols, or disulfonates of alkane-1,3-diols with sodium sulfide. The intramolecular substitution of 3-mercaptalkyl halides or sulfonates is a similar strategy for the preparation of thietanes [12-14]. Alternatively, inter- and intramolecular photochemical [2 + 2] cycloadditions (thia-Paternò–Büchi reactions) of alkenes and thiocarbonyl compounds are another important route for the synthesis of thietanes [15,16], especially, spirothietanes [17,18]. The formal [2 + 2] cycloadditions
of hexafluorothioacetone and olefins are also applied in the preparation of bis(trifluoromethyl)-containing thietanes [19]. The ring-contractions of five and six-membered aliphatic thia-heterocycles have been seldom applied in the preparation of thietraoses [20,21]. In contrast, both nucleophilic and electrophilic ring expansions of thiranes have been developed to synthesize thietanes [22,23]. Phosphorodithioate has been applied in the synthesis of thietanes as a nucleophile and generated phosphorothioate as a leaving group [24]. Some other cyclization methods have been reported in the synthesis of thietanes as well [25] (Figure 2).

This review covers the methods outlined in Figure 2 and also some miscellaneous methods for the synthesis of various thietane derivatives. A special focus is on the construction of the thietane ring, excluding methods for the simple modifications of the thietane rings and their side chains [26–31].

2. Synthesis via cyclic thioetherifications

2.1 Synthesis via double nucleophilic displacements

2.1.1 Synthesis via double nucleophilic displacements of 1,3-dihaloalkanes: Although the double nucleophilic displacements of 1,3-dihaloalkanes with sodium sulfide are the oldest...
methods for the preparation of thietane derivatives and have well been studied, they are widely applied till now. The development of this method before 1965 was reviewed by Sander [12] and this review contains new advances since 1965.

After Sander’s review [12], Cerny and Polacek reported the synthesis of a thietane derivative via the double nucleophilic displacement of 1,3-dichloroalkane in 1966 [32]. They treated 3,5-dichloropentan-2-ol (9) with K₂S to produce 1-(thietan-2-yl)ethan-1-ol (10) in 65% yield (Scheme 1).

![Scheme 1: Synthesis of 1-(thietan-2-yl)ethan-1-ol (10) from 3,5-dichloropentan-2-ol (9).]

In 2007, Nishizono and co-workers used 2,2-bis(bromo-methyl)propane-1,3-diol (11) as starting material to prepare thietanose nucleosides 2 and 14. They first carried out a double displacement with sodium sulfide to obtain thietane-3,3-diylidimethanol (13), which was further converted into two different thietanose nucleosides 2 and 14 [33] (Scheme 2).

![Scheme 2: Synthesis of thietanose nucleosides 2,14 from 2,2-bis(bromo-methyl)propane-1,3-diol (11).]

In the synthesis of sesquiterpene thioalkaloids, the method also was utilized. A double-aldol condensation of methyl crotonate (15) with 1-hydroxymethylbenzotriazole (16) generated methyl 2,2-dihydroxymethylbut-3-enolate (17) in 58% yield. Iodination and subsequent double displacement with sodium sulfide afforded methyl 1-vinylthietane-1-carboxylate (19) in 51% yield over two steps [34]. Compound 19 was used as an intermediate for the total synthesis of sesquiterpene thioalkaloids (Scheme 3).

![Scheme 3: Synthesis of methyl 3-vinylthietane-3-carboxylate (19).]

Spiro[3.3]heptane derivatives were recently used as the surrogates of piperazines, piperidines, morpholines, and thiomorpholines, which display pharmacological activities [35]. 1,6-Thiazaspiro[3.3]heptane (24) was synthesized for discovery of pan-CDK inhibitors. For this, 3-bromo-2,2-bis(bromo-methyl)propan-1-ol (20) was transformed into 3-bromomethyl-3-hydroxymethyl-1-tosylazetidine (21), which was treated with Ph₃P/Br₂ to yield 3,3-bis(bromomethyl)-1-tosylazetidine (22) in 52% yield. The double displacement of 3,3-bis(bromomethyl)-1-tosylazetidine (22) with sodium sulfide followed by the detosylation with Mg in MeOH afforded 1,6-thiazaspiro[3.3]heptane (24) [36] (Scheme 4).

![Scheme 4: Synthesis of 1,6-thiazaspiro[3.3]heptane (24).]

2.1.2 Synthesis via double nucleophilic displacements of disulfonates of alkane-1,3-diols: Considering that 6-amino-3-
azaspiro[3.3]heptane was evaluated as inhibitor of kinases, insecticides, and acaricides, its sulfur analogue, 6-amino-2-thiaspiro[3,3]heptane (28) was prepared from the cheap starting material 2,2-bis(bromo-methyl)propane-1,3-diol (11). Compound 11 was converted into 3-(tert-butoxycarbonyl)-1,1-bis(hydroxymethyl)aminocyclobutane (25) in 6 steps. After the treatment of 25 with methanesulfonyl chloride, the obtained dimethanesulfonate 26 was reacted with sodium sulfide giving rise to 6-(tert-butoxycarbonyl)amino-2-thiaspiro[3,3]heptane (27), which was further transformed into the desired 6-amino-2-thiaspiro[3,3]heptane (28) hydrogen chloride salt after the acidic deprotection [37] (Scheme 5).

During recent decades, the cyclic thioetherification strategy was widely applied in the synthesis of thietane-based square sugars (thietanoses), and sulfur-containing glycomicines of furanoses and pyranoses [38]. The first thietanose was synthesized from vitamin C (29) in 1996 (Scheme 6). Vitamin C (29) was converted first into 1,3-dimesylate 30 of 2,4-di-O-protected 1,2,3,4-butanetetraol in 6 steps. The subsequent treatment with Na2S in refluxing ethanol then gave rise to the protected thietanose 31 in 62% yield [3] (Scheme 6).

Following similar protocols, (S,S)-2,3-bis(benzoyloxymethyl)thietane (34) was synthesized from diethyl L-tartrate (32), which was further converted into thietanocin A (35), a sulfur analogue of oxetanocin A [39] (Scheme 7).

The double displacement cyclic thioetherification strategy was also utilized for the synthesis of thietane-containing spironucleosides. The easily available 5-aldo-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (36) was first treated with formaldehyde in the presence of NaOH followed by MsCl, affording the dimesylate derivative 38, which was reacted with Na2S to afford the spirothietane 39. The latter was further converted into the thietane-containing spironucleoside 40 [40] (Scheme 8).

The same research group synthesized the optically active 2-methylthietane-containing spironucleoside 43 by following a similar synthetic method [40] (Scheme 9).
In 2009, Da Silva and co-worker succeeded in the synthesis of a 4',4'-spirothietane-2',N3-cycloadenosine 46 as a highly constrained analogue of 5'-deoxy-5'-methylthioadenosine. They first prepared tritosylate derivative 44 from D-glucose which was treated with KSAc to give the spirothietane derivative 45. The latter compound was further converted to the final thietane-containing spironucleoside 46 [41] (Scheme 10).

In 2011, Nishizono and co-worker synthesized two anomeric thietanose nucleosides with (Z)-but-2-ene-1,4-diol (47) as the starting material. They first converted the diol 47 into dimethanesulfonates 48 of 1,5-dibenzylxypentane-2,4-diol and treated it with sodium sulfide to afford 2,4-di(benzyl-oxymethyl)thietane (49). Compound 49 was then further transformed into two different anomeric thietanose nucleosides 1 and 50 [4] (Scheme 11).

In the development of novel class I phosphoinositide 3-kinase (PI3k) inhibitors, 6-bromo-3,3-bis(hydroxymethyl)indolin-2-one (51) was reacted first with mesyl chloride and then treated with sodium sulfide to afford 6-bromospiro[indoline-3,3'-thietan]-2-one (53), which was further converted into the target inhibitor candidate 54 [42] (Scheme 12).

2-Methylene-γ-butyrolactone (55) as the initial starting material was converted into bis(hydroxymethyl)quinolizidine 56. After mesylation and the double displacement with sodium sulfide, spirothietane-quinolizidine 57 was obtained as a key
intermediate. It was further applied in the total synthesis of four different natural products of Nuphar sesquiterpene thiopalkaloids 58 and 59 [43] (Scheme 13).

2.2. Synthesis via intramolecular nucleophilic displacements

2.2.1 Synthesis via the direct cyclic thioetherification of γ-mercaptoalkanols: The direct cyclic thioetherification of γ-mercaptoalkanols was regarded as an efficient route to synthesize thietanes. Indeed, the direct cyclization of the 3-mercapto-1-ol unit in 60 with Ph₃P(OEt)₂ as a reagent was realized in the synthesis of the spirothietane derivative 61 [44] (Scheme 14).

Also, 1,3-diols were considered as precursors of γ-mercaptoalkanols. A Japanese group developed a new method to transform 1,3-diols 62 into the precursors of γ-mercaptoalkanols with dibenzoxazol-2-yl disulfide (63) and phosphines. They reacted primary or secondary 1,3-diols 62 with disulfide 63 in the presence of Bu₃P or Ph₃P to selectively synthesize 2-(3-
Scheme 13: Synthesis of the spirothietane 57 as the key intermediate to Nuphar sesquiterpene thioalkaloids.

Scheme 14: Synthesis of spirothietane 61 through a direct cyclic thioetherification of 3-mercaptopropan-1-ol.

Scheme 15: Synthesis of thietanes 66 from 1,3-diols 62.
perchlorate 71 by methylation with dimethyl sulfate and addition of HClO4. After the treatment with KOH powder in MeCN and subsequent hydrolysis it gave thietanylbenzimidazolone 75. In the last step, the hydroxide ion first nucleophilically added to the iminium 71 to generate an O,S-hemiacetal 72. Under the basic conditions, the hemiacetal 72 converted to the thiolate 74, which underwent an intramolecular substitution to give the final product thietanylbenzimidazolone 75 [46] (Scheme 16).

2.2.2 Synthesis via the stepwise nucleophilic displacements:
Besides the double displacements of 1,3-dihaloalkanes with different sulfide salts, thiourea was also used as a nucleophile in the double displacements, actually following the preparation procedure of thiol, affording thietane derivatives. Thiourea reacted with 3,3-bis(chloromethyl)oxetane (76) in the presence of HClO4 to yield S-[2-(3-chloro-2-(chloromethyl)-2-hydroxyethyl)]isothiouuronium perchlorate (77). Heating compound 77 with KOH in ethanol for 40 min yielded 3-chloromethyl-3-hydroxymethylthietane (79) through a thiolate intermediate (78). Further reflux for 16 h gave rise to 2-oxa-6-thiaspiro[3.3]heptane (80) [47] (Scheme 17).

In 1985, Miljkovic and co-workers reported the synthesis of thioanhydrohexopyranosides starting from bromodeoxyglucopyranoside 81. Compound 81 was reacted with p-MeC6H4SO2Cl and KSAc to yield thioacetate 83, that upon treatment with excess NaOMe, gave methyl 2-O-p-toluensulfonyl-4,6-thioanhydro-α-D-gulopyranoside (84), the thietane-containing gulopyranoside [48] (Scheme 18).

For the preparation of thioanhydro sugar derivatives, Cubero and co-workers treated methyl 6-S-acetyl-2,4-di-O-benzoyl-3-O-methanesulfonyl-6-thio-α-D-galactopyranoside (85) with methanolic sodium methoxide to generate methyl 4,6-thioanhydro-α-D-glucopyranoside (89), the thietane-fused pyranoside, in 30% yield [49] (Scheme 19).
Since 2000, a lot of thietane-derived carbohydrates were reported. Voss and co-workers prepared the 2-oxo-7-thiabicyclo[4.2.0]octane derivative (methyl 2,3-di-O-mesyl-4,6-thio-anhydro-α-D-galactopyranoside (93)) from methyl α-D-glucopyranoside (90) through a Mitsunobu thioacetylation, mesylation, thioacetate hydrolysis with the treatment of sodium bicarbonate, and a subsequent intramolecular nucleophilic displacement. In the displacement step, the formation of the four-membered thietane ring is strongly favored over the ring closure between the thiolate and the 2-position, since the S_N2 displacement of a mesylate leaving group adjacent to the anomeric center is known to be restricted [50] (Scheme 20).

The same group synthesized a thietane-fused gulopyranoside starting from methyl 4,6-O-isopropylidene-α-D-glucopyranoside (94). Compound 94 first was mesylated and then hydrolyzed to afford 2,3-dimesylated methyl α-D-glucopyranoside 96. After thioacetylation and treatment with sodium bicarbonate compound 96 was converted into the thietane-fused α-D-gulopyranoside 100. The thioacetate derivative 97 was first converted to the oxirane-fused derivative 98 through an intramolecular substitution. After hydrolysis, the thiolate underwent an intramolecular nucleophilic displacement to generate the final thietane-fused α-D-gulopyranoside 100 [50] (Scheme 21).
In 2004, Schulze and co-workers synthesized 3,5-anhydro-3-thiopentofuranosides 104 from methyl α- and β-arabinosides 101 through a Mitsunobu reaction, mesylation, and hydrolysis sequence followed by an intramolecular displacement. The in situ generated thiolate nucleophilically attacked the mesylate to form the thietane ring [51] (Scheme 22).

Following the similar synthetic route, Polchow and Voss synthesized 4,6-anhydro-4-thiofuranoside 110, 1,3:4,6-dianhydro-1,4-dithio-β-D-sorbofuranoside 112, and 1,3-anhydro-6-S-methyl-1,6-dithio-D-psicofuranoside 113 from 1,2:4,5-di-O-isopropylidene D-fructose (105) [52] (Scheme 23).

In an alternative approach, the thietane ring was constructed more efficiently through a two-step displacement sequence from the D-xylose-derived dimesylate 114 (Scheme 24). The first step displacement involved the selective S_N2 reaction of the primary mesylate with KSAc to yield a monothioacetate 115 in 80% yield. The second displacement was an intramolecular S_N2 process performed under mild basic conditions, affording the desired thietane 116 in 92% yield. After deprotection, oxidative cleavage, and reduction, a thietanose 117 was obtained in 63% overall yield. The thietanose 117 was further applied to synthesize a series of thietanose nucleosides 118 [53]. Similarly, enantiomeric thietanose nucleosides 123 were prepared from L-xylose [53] (Scheme 24).

In 2010, Takahata and co-workers designed and synthesized thietane-fused nucleosides. They first prepared a key intermediate spiro acetal 125, which was converted into two different dimesylated nucleosides. After the deprotection with Hg(OAc)\textsubscript{2} in the presence of TFA, the dimesylated thiols 127 and 130 generated accompanied with the thietane-fused nucleoside 128 in one case. Further the treatment of the dimesylated thiols 127 and 130 with DBU gave rise to the corresponding mesylated thietane-fused nucleosides 129 and 131, which generated the final thietane-fused nucleosides 129 and 132 after the reactions with benzoic acid and CsF and subsequent aminolysis [54] (Scheme 25).

The methyl 2,3-anhydro-α- and β-D-ribofuranosides 133 were used as starting materials and converted into 3,5-anhydro-3-
Scheme 24: Synthesis of optically active thietanose nucleosides from D- and L-xyloses.

Scheme 25: Synthesis of thietane-fused nucleosides.
thiopentofuranosides 135 through a Mitsunobu reaction with thiolacetic acid and hydrolysis followed by an intramolecular nucleophilic ring-opening of the oxirane ring. The newly generated thiolate underwent a nucleophilic ring-opening of the oxirane to generate the thietane ring [55] (Scheme 26).

After the ring-opening of methyl 2,3-anhydro-α-D-ribofuranoside (133a) with NaOMe, following a sequence of a Mitsunobu reaction, mesylation, and treatment with sodium bicarbonate, another 3,5-anhydro-3-thiopentofuranoside 138 was prepared [51] (Scheme 26).

The 2-amino-3,5-anhydro-3-thiofuranoside 141 was prepared from methyl 2,3-anhydro-α-D-ribofuranoside (133a), which was first reacted with sodium azide followed by the similar synthetic route as described above, affording 3,5-anhydro-2-azido-3-thiofuranoside 139. The azido derivative 139 generated the final product 2-amino-3,5-anhydro-3-thiofuranoside 141 by reduction with triphenylphosphine [55] (Scheme 27).

2.2.3 Synthesis via the nucleophilic ring-opening of three-membered heterocycles and subsequent displacement from halomethyloxirane derivatives: Chloromethyloxirane (142a) and its 2 and 3-phenyl derivatives 142b and 142c reacted with H$_2$S in the presence of Ba(OH)$_2$ to give the corresponding thietane-3-ols 145. In this reaction H$_2$S first was deprotonated to the hydrogensulfide anion (−SH) by Ba(OH)$_2$. The obtained anion nucleophilically attacked the less sterically or benzylic ring carbon atom of the oxirane ring, giving mercaptopentanolates 143. A proton transfer generated hydroxyalkanethiolates 144 because the acidity of the thiols is higher than that of alcohols, the newly generated thiolates 144 underwent an intramolecularly nucleophilic displacement to give thietane-3-ols 145 [56] (Scheme 28).

Scheme 26: Synthesis of 3,5-anhydro-3-thiopentofuranosides.

Scheme 27: Synthesis of 2-amino-3,5-anhydro-3-thiofuranoside 141.

Scheme 28: Synthesis of thietane-3-ols 145 from (1-chloromethyloxiranes 142 and hydrogen sulfide.

In a similar approach, chloromethyloxirane (142a) was first converted into a thietan-3-ol 145a by treatment with H$_2$S and Ba(OH)$_2$. Compound 145a was further transformed to...
3-aminothietane-3-carboxylic acid (146), a modulator of the N-methyl-D-aspartate (NMDA) receptor [57] (Scheme 29).

Several thietane-3-ol derivatives 145 were synthesized in low to good yields by the reaction of 2-(1-haloalkyl)oxiranes 142 and 147 with ammonium monothiocarbamates 148 as the sulfur nucleophiles. First, a nucleophilic ring-opening of the oxiranes 142 and 147 by monothiocarbamates 148 gave rise to the S-(γ-halo-β-hydroxyalkyl)carbamates 149 with release of amines. The latter then aminolyzed the carbamates 149 to generate ureas 151 and γ-halo-β-hydroxyalkanethiols 150. The intermediates 150 further underwent an intramolecular cyclization to produce the thietane-3-ols 145 in low to good yields [58] (Scheme 30).

Paclitaxel (Taxol®) and docetaxel (Taxotere®) both are anticancer drugs of the taxoid series. They inhibit cell growth through the interaction with microtubules. In order to study the structure–activity relationships, the D-ring-modified deoxythiataxoid 154a was synthesized. For this, the iodomethyloxirane derivative 152 was first treated with lithium sulfide followed by reaction with carbonyldiimazole (CDI), yielding the thietane derivative 153 and byproduct. The thietane derivative 153 was then converted into 7-deoxy-5(20)-thiapaclitaxel 154a in a three steps sequence [59] (Scheme 31).

Scheme 30: Synthesis of thietane-3-ols 145 from 2-(1-haloalkyl)oxiranes 142 and 147 with ammonium monothiocarbamates 148.
Another member of taxoids, 10-deacetylbaccatin III (155) was isolated from the leaves of the European yew tree *Taxus baccata* L. in a significant yield and was applied as starting material for the semisynthesis of 5(20)-thiadocetaxel 158. First, the compound was converted into the corresponding bromomethyloxirane derivative 156, which generated the corresponding thietane-fused product 157 by the treatment with KSAc. Product 157 was finally transformed to 5(20)-thiadocetaxel 158 [6] (Scheme 32).

### 2.2.4 Synthesis via the nucleophilic ring-opening of threemembered heterocycles and subsequent displacement from oxirane-2-methyl sulfonates:

Similar as for the halomethyloxirane derivatives, oxiranemethyl mesylate derivatives were also used as precursors for the synthesis of the corresponding thietane derivatives. After various protection–deprotection steps and mesylation, the oxiranemethyl mesylate derivatives 160 were prepared (Scheme 33). Following treatments with KSAc and NaOMe in methanol, respectively, the corresponding

![Scheme 32: Synthesis of 5(20)-thiadocetaxel 158 from 10-deacetylbaccatin III (155).](image)

![Scheme 33: Synthesis of thietane derivatives 162 as precursors for deoxythiataxoid synthesis through oxiranemethyl mesylate derivatives 160.](image)
thietane-fused products 162 were obtained as the intermediates for the synthesis of deoxythiataxoids [60] (Scheme 33).

Taxine B (163a) and isotaxine B (163b) were obtained from the leaves of the European yew tree Taxus baccata L. in significant yields as well. The compounds were used for the semisynthesis of further sulfur derivatives of taxoids by first converting them into the acetal-protected oxiranemethyl mesylate derivative 164. After the treatment of compound 164 with KSAc, the mesylate 165 generated the corresponding thietane-fused product 166, which was finally converted into the D-ring-modified 7-deoxy 5(20)-thiadocetaxel 154b [6] (Scheme 34).

The mechanism for the formation of thietane rings 171 from oxiranes 167 with vicinal leaving groups was suggested as a nucleophilic ring-opening and intramolecular transesterification followed by an intramolecular displacement [6] (Scheme 35).

2.2.5 Synthesis via the nucleophilic ring-opening of three-membered heterocycles and subsequent displacement from thiirane-2-methanol derivatives: Gay and Scherowsky prepared thietane derivatives from a thiirane-2-methanol when they worked on the synthesis of liquid crystal materials. They synthesized a chiral thietane 175 from the chiral thiirane-2-methanol 172 with 3-nitrophenol (173) under Mitsunobu conditions (Scheme 36). In the synthesis, the alcohol 172 first reacted with triphenylphosphine to generate thiirane 174, which underwent nucleophile ring-opening followed by an intramolecular substitution to afford chiral thietane 175 [61].

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\text{Scheme 34: Synthesis of 7-deoxy 5(20)-thiadocetaxel 154b.}
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\text{Scheme 35: Mechanism for the formation of the thietane ring in 171 from oxiranes with vicinal leaving groups 167.}
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2.2.6 Synthesis via the nucleophilic ring-opening of three-membered heterocycles and subsequent displacement from aziridine-2-methyl tosylate: (1R,2S,6R)-6-Methyl-7-tosyl-7-azabicyclo[4.1.0]heptan-2-yl tosylate (179) is a derivative of aziridine-2-methyl tosylate. After the ring-opening with ammonium tetrathiomolybdate and subsequent intramolecular cyclization, the compound was converted into a bridged thietane 183 in 75% yield. The results indicated that, in the ring-opening step, tetrathiomolybdate nucleophilically attacked the more substituted aziridine carbon atom [62] (Scheme 37).

3. Synthesis via cycloadditions

Cycloadditions, especially the photochemical [2 + 2] cycloaddition (thia-Paternò–Büchi reaction) of thiones and thioamides with olefins [15-18], and formal cycloadditions are alternative routes for the construction of thietane derivatives, especially multisubstituted thietanes.

3.1 Synthesis via photochemical [2 + 2] cycloadditions

3.1.1 Synthesis via intermolecular photochemical [2 + 2] cycloadditions: In 1969, the first photo-assisted [2 + 2] cycloadditions of alkenes and thiocarbonyl compounds were applied for the synthesis of thietanes. Later, this transformation was considered as thia-Paternò–Büchi reaction. The reactions of thiobenzophenone (184a) with both, electron-rich olefins 185, 186a, and 187a under irradiation with UV light at 366 nm, and electron-deficient olefins 187b,c, 188, and 189 under irradiation with either 366 nm or 589 nm UV light gave the desired thietanes 190–195 with retention of the olefin configuration in most cases. An exception was observed for the reaction of 184a with (Z)-prop-1-enylbenzene [(Z)-185], which generated a mixture of cis- and trans-thietanes, cis-190 and trans-190, both configuration retention and inversion products [63].
(Scheme 38). However, some olefins, such as cyclohexene, oct-1-ene, vinyl ether, vinyl sulfide, etc., produced 1,4-dithiane derivatives as products through the reaction of two molecules of thiobenzophenone (184a) and one molecule of the olefin under irradiation with 589 nm UV light [63].

In 1978, Gotthardt and Nieberl investigated the UV light-induced [2 + 2] cycloaddition reaction of thiones with cyclic alkenes and realized the synthesis of spirothietane derivatives. Under $n \rightarrow \pi^*$ excitation using Na light, xanthione (196) reacted withacenaphthylene (197), indene (198), or N-phenylmaleimide (199) with the formation of the corresponding spirothietane derivatives 200–202 in good yields. The analogous photoreactions of 2-thioparabanate (203) in the presence of indene (198), benzo[b]furan (204), or N-phenylmaleimide (199) gave spirothietanes 205–207 as well [64] (Scheme 39).
The irradiation of a 0.050 mol/L solution of thioxanthenethione (208) in CH₂Cl₂ with butatrienes Me₂C=C=C=CR₁ 209 through a K₂Cr₂O₇ filter solution gave 70 to > 90% yields of the corresponding spirothietanes 210 [65] (Scheme 40).

The same research group also performed the reaction mechanistic studies. The reactivity of the substituted allenes towards triplet aromatic thiones was investigated. The product analysis revealed the formation of thietanes and occasionally of [4 + 2] cycloadducts (thiopyrans) generally in high overall yields. Steady-state measurements showed that electron-donating substituents present in the allenes enhanced the overall reaction rate. There was little effect of the solvent polarity on the reaction rate. The formation of thietanes involved the excited triplet thiones and the π-bond of allenes [66].

In 1984, Bos and co-workers realized the photocycloaddition reaction of the first stable thiobenzaldehyde, 2,4,6-tri(tert-butyl)thiobenzaldehyde (211) with substituted allenes 212. Irradiation of thiobenzaldehyde 211 with RCR₁=CH₂ 212 gave diastereospecific [2 + 2] cycloadducts, thietanes 213 in 75–95% yields [67] (Scheme 41).

In 1984, Coyle and Rapley performed the photochemical cycloadditions of N-methylthiophthalimide (214) with 2,3-dimethylbut-2-ene (215a) or with stilbene (186b) to give spirothietanes 216 and 217, respectively [68] (Scheme 42).
In 1985, Jenner and Papadopoulos prepared fused thietane derivatives 220 by the photo [2 + 2] cycloaddition of quadricyclane 218 with thiocarbonyl derivatives 219. With carbon disulfide, mono- and bicycloaducts 221 and 222 were formed depending on concentration, temperature, and pressure conditions [69] (Scheme 43).

In the same year, Kanaoka and co-workers reported the intermolecular photo [2 + 2] cycloadditions of N-methylthiosuccinimides 223 and N-methylthiophthalimide (225) with alkenes 215 and a conjugated diene 226, generating spirothietanes 224, 227–229, 231, 232, and 234. In some cases, the reverse [2 + 2] cycloaddition occurred with the loss of a molecule of thioacetone [70] (Scheme 44).

The photoreaction of N-methylthiosuccinimide (236) with 2,3-dimethyl-2-ene (215a) gave rise to a mixture of thietane and oxetane derivatives 238 and 239, with thietane 238 as the major component. However, the reaction of the aromatic counterpart, N-methylmonothiophthalimide (237a) with olefins 215a and 186b, produced exclusively thietane derivatives 240 and 241 [70] (Scheme 45).

The authors further investigated photoreactions of N-substituted monothiophthalimides 237 with styrene derivatives 186 and 242, affording the corresponding spirothietanes 243 and 244 [71] (Scheme 46).

They also documented the photocycloaddition of ring-substituted cyclic dithiosuccinimides 223 with 2,3-dimethyl-2-butene (215a), affording a series of spirothietanes 245 [72] (Scheme 47).

In 1986, Coyle and Rapley reported that the photochemical cycloaddition reactions of N-methylthiophthalimide (237a) and N-methylthiophthalimide (225) with alkenes worked as well [73].

In 1987, Ooms and Hartmann showed the photochemical [2 + 2] cycloaddition of diaryl thione 184b with ketene acetals 247 [74] (Scheme 48).

In the same year, Nishio studied the photocycloadditions of nitrogen-containing cyclic thiones 249 and 250 with 2-methylacrylnitrile (251a) and methyl 2-methylacrylate (251b), respec-
Scheme 44: Synthesis of tricyclic thietanes via the photo [2 + 2] cycloaddition of N-methylthiosuccinimides or N-methylthiophthalimide with olefins.
Scheme 45: Synthesis of tricyclic thietanes via the photo [2 + 2] cycloaddition of N-methylthiosuccinimide/thiophthalimide with olefins.

Scheme 46: Synthesis of tricyclic thietanes via the photo [2 + 2] cycloaddition of N-alkylmonothiophthalimides with styrene derivatives.

Scheme 47: Synthesis of spirothietanes from dithiosuccinimides with 2,3-dimethyl-2-butene (215a).

Scheme 48: Synthesis of thietanes 248a,b from diaryl thione 184b and ketene acetal 247a,b.

Scheme 49: Photocycloadditions of acridine-9-thiones and pyridine-4(1H)-thione (250) with 2-methylacrylonitrile (251a) and methyl 2-methylacrylate (251b).
In 1989, Kanaoka and co-workers further studied the photo [2 + 2] cycloadditions of thiobarbiturates 256–258, whose skeletons consisted of a combination of a thioamide and an amide or a thioamide (two-imides system), and olefins. 2-Thiobarbiturate 256 generated both, the spirotetanes 259, 261, and 263 and the corresponding cycloreversion products 260, 262, and 264. When compound 256 was reacted with 2,3-dimethylbut-2-ene (215a), the spirothetane 259 was formed in slight excess. However, the cycloreversion products 262 and 264 formed preferably, in the reaction of 256 with ethyl vinyl ether (215e) and propen-2-ylbenzene (186a). Notably, the photoreaction of 2,4-dithiobarbiturate 257 and 2,3-dimethylbut-2-ene (215a) produced exclusively the 4-thietane derivative 265 in 91% yield. 2,4,6-Trithiobarbiturate 258 reacted with the same olefin to yield the corresponding 4-thietane derivative 266 accompanied with dithiouracil derivative 267 as byproduct [76] (Scheme 50).

Rao and Ramamurthy systematically investigated the intermolecular photocycloadditions of 1,1,3-trimethyl-2-thioxo-1,2-dihydronaphthalene (268) with a series of electron-deficient olefins 187b,c, 189, 242a, and 269–272. The reactions afforded stereospecifically and regioselectively the 3-functionalized spirotetanes 273–285 as the major products. The stereospecific addition suggested either a concerted process or a pathway involving very short-lived diradicals as intermediates. To explain the regioselectivity, theoretical calculations were performed with thiocoumalone and acrylonitrile as model substrates. For the frontier molecular orbital treatment, the largest coefficients in both HOMO and LUMO of thiocoumalone existed on the sulfur atom, while the largest coefficients in both HOMO and LUMO of acrylonitrile were located at the $\beta$-carbon atom. These favored the overlapping between the sulfur atom and the $\beta$-carbon atom, deciding the regioselectivity [76, 77] (Scheme 51).

Interestingly, the photochemical behavior of thioenones was obviously different from that of enones. The latter underwent the [2 + 2] annulation with olefins at their olefinic center to yield cyclobutane derivatives, and rarely undergo oxetane formation completely. The reaction parameters such as solvent affected the balance between the cyclobutane and oxetane formation. Whereas reactions of olefins with thioenones took place on the thiocarbonyl group to give stereospecific and regioselective thietane derivatives.

Scheme 50: Synthesis of thietanes via the photo [2 + 2] cycloaddition of mono-, di-, and trithiobarbiturates 256–258 with olefins.
Scheme 51: Synthesis of spirothietanes via the photo [2 + 2] cycloaddition of 1,1,3-trimethyl-2-thioxo-1,2-dihydronaphthalene (268) and olefins.
The same group further studied the photo [2 + 2] cycloadditions of thiocoumarin (286) and alkenes 187, 215a,f, and 271, producing the corresponding spirothietane derivatives 287–291 [78] (Scheme 52).

In 1988, Kanaoka et al. studied the photochemistry of semicyclic and acyclic thioimides 292–294 and 295 with 2,3-dimethylbut-2-ene (215a) afforded the corresponding thietanes 296–299. However, the products were obtained together with pyrrolidinone, thiooxopyrrolidinone, or thio benzamides as byproducts. The latter were generated in the competition between Paternò–Büchi-type and Norrish-type I reactions [79] (Scheme 53).

In the same year, Nishio and co-workers, investigated the photochemical [2 + 2] cycloadditions of indoline-2-thiones with cyanoalkenes. Only 2-alkylideneindolines were obtained via a ring cleavage of the thietanes, that had formed in the [2 + 2] photocycloaddition of the thiocarbonyl moiety and the olefin. However, the reaction of 1,3,3-trimethylindoline-2-thione (300) and isobutene (215c) afforded the corresponding spiroindoline-thietane derivative 301 [80] (Scheme 54).

They further investigated the photochemical [2 + 2] cycloadditions of alkyl and aryl 2-thioxo-3H-benzoazole-3-carboxylates 302 and alkenes 215a,b, 251a, and 227, affording the corresponding spirobenzoxazole-thietane derivatives 303 [81-84] (Scheme 55).

Scheme 52: Synthesis of spirothietanes via the photo [2 + 2] cycloaddition of thiocoumarin 286 with olefins.

Scheme 53: Photochemical synthesis of thietanes 296–299 from semicyclic and acyclic thioimides 292–295 and 2,3-dimethylbut-2-ene (215a).

Scheme 54: Photochemical synthesis of spirothietane 301 from 1,3,3-trimethylindoline-2-thione (300) and isobutene (215c).
Upon the irradiation of tetrahydrotrimethylthioxo and [3-oxo-1-thioxo or 1-oxo-3-thioxo]isoquinolines 306 and 307 with olefins 215a, b, and 186c or indene (198), the regioselective [2 + 2] cycloaddition occurred to give oxo- or thiooxospiro-[isoquinoline-1,2'(or 3,2')-thietane] derivatives 208–310. In some cases, the products were accompanied with the related alkylidenetetrahydrotrimethylthioxoisouquinolines as the by-products [85] (Scheme 56).

Similar intramolecular photoreactions of N-alkenylthiohomophthalimides were attempted as well, affording the tetracyclic thietane-fused isoquinoline derivatives regioselectively [86].

The reactions of isobenzofuran-1-thiones 311 and 2-benzothiophene-1-thiones 314 with 2,3-dimethylbut-2-ene (215a) gave the corresponding spirothietanes 312 and 315 under photo irradiation. The spirothietanes 312 derived from 3-unsubstituted or 3-monosubstituted 1,3-dihydroisobenzofuran-1-thiones 311 were less stable and underwent a thermal rearrangement to generate tricyclic isobenzofurans 313 through the ring-cleavage of the thietanes. It was assumed that the rearrangement was assisted through participation of the oxygen lone-pair electrons [17] (Scheme 57).

The silicon-containing phenyl triphenylsilyl thioketone (316) reacted with electron-poor olefins, such as acrylonitrile (187b), methyl acrylate (187c), and cis- and trans-1,2-dichloroethenes 188, under photochemical conditions, giving 2-silylthietanes 317 and 318 in a regio- and highly stereoselective manner. However, silyl thietanes without any regio- or stereocontrol
Scheme 57: Synthesis of spirothietanes from 1,3-dihydroisobenzofuran-1-thiones 311 and benzothiophene-1-thiones 314 with 2,3-dimethylbut-2-ene (215a).

In 2003, Sakamoto and co-workers investigated the intermolecular diastereoselective photo [2 + 2] cycloaddition of axially chiral monothiosuccinimides 319 which could enantiomerize into both (R) and (S)-isomers, and 1,1-diphenylethene (216c) under UV irradiation. As the products spirothietane-pyrrolidonones 320 were obtained in 65–89% yield. The diastereoselectivity was controlled by the steric effect of the ortho-substituents on the phenyl ring [88] (Scheme 59).

The intermolecular photochemical [2 + 2] cycloaddition of tert-butyl 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetate (322) and thiobenzophenone (184a) was applied to prepare thietane 323 as a model compound for photolyses in a comparative flavin-induced cleavage study of oxetanes and thietanes [89] (Scheme 60).

2,5-Diphenylsilacyclopentadiene (324) underwent a photo-induced [2 + 2] cycloaddition with CS₂ to afford two regioiso-
Scheme 60: Synthesis of bicyclic thietane 323 via the photo [2 + 2] cycloaddition of 2,4-dioxo-3,4-dihydropyrimidine 322 and thiobenzophenone (184a).

Scheme 61: Photo-induced synthesis of fused thietane-2-thiones 325 and 326 from silacyclopentadiene 324 and carbon disulfide.

Scheme 62: Synthesis of highly strained tricyclic thietanes 328 via the intramolecular photo [2 + 2] cycloaddition of allyldithiosuccinimides 327.

Scheme 63: Synthesis of tri- and pentacyclic thietanes 330 and 332, respectively, through the intramolecular photo [2 + 2] cycloaddition of allyldithiosuccinimides 329 and 331.

Scheme 64: Synthesis of tricyclic thietanes 334 via the intramolecular photo [2 + 2] cycloaddition of N-vinylthiazolethiones 333.

Scheme 65: Synthesis of pyridoisoindolones 337 via the intramolecular photo [2 + 2] cycloaddition of N-but-3-enylthiophthalimides 335.

3.1.2 Synthesis via intramolecular photochemical [2+2] cycloadditions: In 1985, Machida’s group reported the intramolecular photo-assisted [2 + 2] cycloadditions of N-allylthiosuccinimides 327 applying 1 kW high-pressure mercury lamp irradiation under a nitrogen atmosphere, giving the highly strained tricyclic thietanes 328 [91] (Scheme 62).

In 1987, Wipf and Heimgartner realized the photochemical intramolecular [2 + 2] cycloaddition of vinylthiazolethiones 333 to give tricyclic thietane derivatives 334 in 38–88% yields [93] (Scheme 64).

In 1992, Oda’s group found that, under photo irradiation conditions N-but-3-enylthiophthalimides 335 underwent an intramolecular photo-assisted [2 + 2] cycloaddition first giving tricyclic thietanes 336, which further photochemically converted into pyridoisoindolones 337 [94] (Scheme 65).

To synthesize various pyrrolizidine alkaloids, Padwa’s group used the intramolecular photocycloaddition of N-but-3-enyl-5-thiopyrrolidin-2-ones 338. The intramolecular photo [2 + 2] cycloadditions first generated the tricyclic thietanes 339, which further underwent a ring-opening reaction to afford...
Scheme 65: Synthesis of tricyclic thietanes via the intramolecular photo [2 + 2] cycloaddition of N-but-3-enylthiophthalimides and photochemical conversion to pyridoisoindolones.

Nishio and co-workers investigated the photochemical [2 + 2] cycloaddition of vinyl 2-thioxo-3H-benzoxazole-3-carboxylate, affording the corresponding tetracyclic fused benzoxazolethietane derivative in 20% yield [83] (Scheme 69).

Similarly, linear and cyclic 3-but-3-enylpyrrolidin-2,5-dithiones gave tricyclic and tetracyclic fused thietane derivatives under photo irradiation [95] (Scheme 68).

In 1991, Sakomto and co-workers started on the synthesis of highly rigid thietane-fused β-lactams. They prepared various derivatives in high yields via the photochemical cycloaddition reactions of N-(α,β-disubstituted alkyl-2-enyl)thiobenzamides. Some thioamides, (i.e., R = CHMe₂), formed...
R^2=CH=CR^1CONHCMetCSPh via a β-H abstraction of the thio-carbonyl group. Substituents at the α-position to the alk-2-enoyl moiety led to a preference for the [2 + 2] cyclization over the β-H abstraction. The reaction was shown to proceed via an n-π* triplet-excited state [96] (Scheme 70).

In 1993, the same group first attempted to prepare a chiral thietane-fused β-lactam 356a from an achiral monothioimide 355a using a chiral crystal environment through a topocemically controlled intramolecular photochemical [2 + 2] cycloaddition. The reaction afforded the product in 70% yield with 40% ee at −45 °C and in 75% yield with 10% ee at 0 °C, respectively [97] (Scheme 71).

One year later, they studied the diastereoselective synthesis of highly rigid thietane-fused β-lactams 358–361 from a chiral monothioimide 357. The photochemical [2 + 2] cycloaddition reaction was performed both in benzene solution and in the solid state, affording 78% yield with a ratio of syn/trans 8.7:1 and 61% de for syn-isomers at 15 °C in crystals, while no diastereoselectivity could be observed in benzene solution [16] (Scheme 72).

In 2001, they performed the absolute asymmetric synthesis of highly rigid thietane-fused β-lactams 356 from achiral monothioimides 355 using a chiral crystal environment through a
Scheme 72: Diastereoselective synthesis of the thietane-fused \(\beta\)-lactams via the intramolecular photo [2 + 2] cycloaddition of the chiral monothioimide 357.

Scheme 73: Asymmetric synthesis of thietane-fused \(\beta\)-lactams via the intramolecular photo [2 + 2] cycloaddition of monothioimides 355.

Scheme 74: Synthesis of the bridged bis(trifluoromethyl)thietane from 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and quadricyclane (218).
Scheme 76: Synthesis of bis(trifluoromethyl)thietanes from 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and electron-rich olefins.

The reaction of 2,2,4,4-tetrafluoro-1,3-dithietane (363) with 1,1-dimethylthioethene (377) generated 2,2-dimethylthio-4,4-di(trifluoromethyl)thietane (378) in 80% yield [100] (Scheme 77).

Scheme 77: Synthesis of 2,2-dimethylthio-4,4-di(trifluoromethyl)thietane (378) from 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and 1,1-dimethylthioethene (377).

A recent mechanistic investigation revealed that the CsF catalyst was not required. The solvent, such as DMSO (379), nucleophilically attacked the 1,3-dithietane 363, resulting in ring opening and further formation of bis(trifluoromethyl)thioacetone (381). The latter reacted with olefins 371 to afford thietanes 374. The reaction of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) with alkyl vinyl ethers 371 or phenyl vinyl sulfide (372b) in DMSO at 70 °C afforded the corresponding 2,2-bis(trifluoromethyl)-3-alkoxy/phenylthiothietanes 374 and 375b, respectively, with 1,3-dithiolanes 382 as byproducts [101] (Scheme 78).

The reactions of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and styrenes 383 produced the [2 + 2] adducts 4aryl-2,2-bis(trifluoromethyl)thietanes 384 and Diels–Alder adducts 385, which further reacted with another molecule of bis(trifluoromethyl)thioketone (381) to yield the double Diels–Alder adducts 385 and thiocromane derivatives 386, respectively, through another Diels–Alder reaction and an ene reaction [101] (Scheme 79).
Scheme 79: Synthesis of 2,2-bis(trifluoromethyl)thietanes from 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and styrenes (383) in DMSO.

Scheme 80: Synthesis of the bridged bis(trifluoromethyl)thietane 364 from 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (363) and quadricyclane (218) in DMSO.

Scheme 81: Synthesis of 2,4-diiminothietanes (390) from alkenimines and 4-methylbenzenesulfonyl isothiocyanate (389).

Scheme 82: Synthesis of arylidene 2,4-diiminothietanes (393) starting from phosphonium ylides (391) and isothiocyanates.
Scheme 83: Synthesis of thietane-2-yldieneacetates 397 through a DABCO-catalyzed formal [2 + 2] cycloaddition of benzyl allenoate (395) and dithioesters 394.

1,4-oxathiones 396 with benzyl thietane-2-yldieneacetates 397 as byproducts [104] (Scheme 83).

4. Synthesis via the ring expansions and contractions
4.1 Synthesis via ring expansion
The ring expansions of thiiranes are alternative ways to prepare thietane derivatives. The transformations included the nucleophilic ring expansion of (1-haloalkyl)thiiranes with various nucleophiles, nucleophilic ring expansion of thiiranes with sulfur ylides, and the electrophilic ring expansion of thiiranes with carbenes generated from sulfur ylides under the catalysis of transition-metal catalysts.

4.1.1 Synthesis via nucleophilic ring expansion of 2-(1-haloalkyl)thiiranes: A thirane–thietane rearrangement took place upon the interaction of (1-haloalkyl)thiiranes 398 with hard and weak nucleophiles (:Nu−) in the presence of a base. It was an efficient method for the preparation of 3-substituted thietanes 400 from (1-haloalkyl)thiiranes 398 through an intramolecular nucleophilic substitution followed by an intermolecular nucleophilic displacement with the in-situ generated 1-thiabicyclo[1.1.0]butan-1-iums 399 as key intermediates. Following this route, 3-substituted thietanes 400 were prepared from reactions of 2-(1-chloroalkyl)thiiranes 398, especially chloromethylthiirane (epithiochlorohydrin, 398a), with hard and weak nucleophiles [105-109], including phenoxides [105], carboxylates and dicarboxylates [106,107], potassium cyanide, sodium azide, hydroxylamine, trifluoromethanesulfonamide, and pyridine [108]. However, the method could only applied to the synthesis of 3-substituted thietanes 400 from (1-chloroalkyl)thiiranes 398 (Scheme 84).

The treatment of various N-substituted sulfonamides 405 with chloromethylthiirane (398a) in the presence of KOH in water.

Scheme 84: Synthesis of 3-substituted thietanes 400 from (1-chloroalkyl)thiiranes 398.

Nitrogen-containing aromatic heterocycles, such as 2-chloro-5(6)-nitrobenzimidazole (401) and 3,5-dibromo-1,2,4-triazole (402), were used as nucleophiles in the reaction with chloromethylthiirane (398a) giving rise to 3-heteroarylthietanes 403 and 404, respectively [109,110] (Scheme 85).

The treatment of various N-substituted sulfonamides 405 with chloromethylthiirane (398a) in the presence of KOH in water.

Scheme 84: Synthesis of 3-substituted thietanes 400 from (1-chloroalkyl)thiiranes 398.
gave rise to the corresponding 3-sulfonamidothietanes 406 in low to moderate yields [111] (Scheme 86).

Also isatins 407 reacted with chloromethylthiirane (398a) to afford N-(thietane-3-yl)isatin derivatives 408 in moderate yields [112] (Scheme 87).

When weakly nucleophilic nitrophenols 409 were used as nucleophiles, the ring-expansion reaction of chloromethylthiirane (398a) yielded the corresponding 3-(nitrophenyloxy)thietanes 410 in only low to moderate yields under basic conditions [113] (Scheme 88).

Similarly, various N-arylcyanamides 411 reacted with chloromethylthiirane (398a) under basic conditions to give the corresponding N-aryl-N-(thietane-3-yl)cyanamides 412 in moderate to good yields [113] (Scheme 89).

Pyrimidine-2,4(1H,3H)-diones 413 were derivatized with chloromethylthiirane (398a), giving rise to 1-(thietane-3-yl)isatins 408 from chloromethylthiirane (398a) and isatins 407.
4.1.2 Synthesis via nucleophilic ring expansion of thiiranes:
The nucleophilic ring expansion of thiiranes was used for the synthesis of thietanes. Isocyanooalkanes 415 can be considered as nucleophiles. However, after the nucleophilic addition, they could become electrophiles. Thus, they can be applied in the nucleophilic ring expansion of thiiranes 416, in which the generated thiolates 417 as nucleophiles undergo a further intramolecular addition to form iminothietanes 418. 2-Iminothiiranes 416 underwent a nucleophilic ring expansion with isocyanooalkanes 415 as nucleophiles to give rise to 2,4-diiminothietanes 418 in 33 to 52% yields [101] (Scheme 91).

3-Chloroallyl lithium (420) was also applied as a nucleophile to synthesize 2-vinylthietanes 421 in the electrophilic ring expansion of thiiranes 419. The corresponding thiiranes 419 reacted with 3-chloroallyl lithium (420), yielding vinylthietanes 421 in 10–73% yields. This was a general route towards the synthesis of 2-vinylthietanes 422. From a mechanistic point of view, 3-chloroallyl lithium (420) first coordinated with the thiiranes 419 followed by a nucleophilic ring opening and intramolecular substitution [115] (Scheme 92).

One carbon-containing nucleophiles with a good leaving group should be another reagent for the nucleophilic ring expansion of thiiranes. In the ring expansion, the nucleophiles first nucleophilically open the thiiranes and the generated thiolates then serve as nucleophiles to undergo a further intramolecular displacement to give the thietanes. Dimethyloxosulfonium methylide was demonstrated to be a suitable reagent for the nucleophilic ring expansion of three-membered heterocycles. It was successfully applied in the preparation of oxetanes and azetidines via the ring expansions of oxiranes [116-118] and aziridines [119,120]. However, both thiiranes and thietanes were less stable than the corresponding oxa and aza-analogs.
Thiiranes 419 were readily prepared from the corresponding oxiranes [121-123]. The ring expansion reactions of trimethyloxosulfonium iodide (424) and various thiiranes 419 delivered the corresponding thietanes 425 in the presence of NaH in a mixture of THF and DMSO at 40 °C [22] (Scheme 93).

The reaction mechanism was proposed as following. The treatment of trimethyloxosulfonium iodide (424) with sodium hydride generated dimethyloxosulfonium methylide (426) as the one carbon-containing nucleophile with DMSO (379) as a good leaving group. The nucleophilic attack of 426 on thiiranes 419 from the least substituted ring carbon atom generated the zwitterionic intermediates 427, with a good regioselectivity following the general regioselectivity rule in nucleophilic ring opening reactions of aliphatic three-membered heterocycles [124-132]. The generated thiolate in the zwitterionic intermediates 427 then further underwent an intramolecular nucleophilic substitution to yield the desired thietanes 425 by loss of a molecule of DMSO [22] (Scheme 94).

**Scheme 93:** Synthesis of thietanes from thiiranes 419 and trimethyloxosulfonium iodide 424.

| R¹ | R² | yield (%) | R¹ | R² | yield (%) |
|----|----|-----------|----|----|-----------|
| H  | PhOCH₃ | 62        | H  | 4-MeC₆H₄OCH₂ | 75        |
| Me | PhOCH₂ | 63        | Me | 4-MeC₆H₄OCH₂ | 59        |
| H  | PhCH₂ | 63        | H  | PhCH₂CH₂OCH₂ | 74        |
| Me | 4-ClC₆H₄OCH₂ | 38    | Me | 4-ClC₆H₄SCH₂ | 18        |
| H  | PhCH₂ | 63        | H  | n-Hex     | 72        |
| Me | 4-MeC₆H₄OCH₂ | 91    | Me | 3-MeC₆H₄OCH₂ | 92        |
| Me | 4-O₂NC₆H₄OCH₂ | 17    | Me | PhCH₂CH₂ | 52        |

4.1.3 Synthesis via electrophilic ring expansion of thiiranes:

To realize the synthesis of functionalized thietanes, electron-deficient sulfur ylides were investigated in the ring expansion of thiiranes. However, the reactions failed due to the poor nucleophilicity of the electron-deficient sulfur ylides. However, in the presence of rhodium catalysts, the electron-deficient sulfur ylides were converted into electrophilic metallocarbenes, which favorably reacted with the electron-rich sulfur atom in the thiiranes and further underwent an electrophilic ring expansion to afford thietanes.

Dimethylsulfonium acylmethylides 428 reacted with 2-alkylthiiranes 419 to produce 2-acyl-4-alkylthietanes 429 and 430 in moderate to good yields. However, they gave rise to mixtures of 2-acyl-4-arylthietanes 432 and 2-acyl-3-arylthietanes 433 in ratios between 1:4 to 1:10 in the reactions with 2-arylthiiranes 431 [23] (Scheme 95).

The reaction mechanism was proposed as following. The nucleophilic acyl sulfur ylides 428 first reacted with the rhodium catalyst to generate the electrophilic metallocarbenes 434 by loss of dimethyl sulfide, realizing an umplung. Thiiranes 419 then reacted nucleophilically with the electrophilic metallocarbenes 434 to yield thiiranium intermediates 435, which were nucleophilically attacked by the released dimethyl sulfide, producing the ring-opened zwitterionic intermediates 436. The intermediates 436 further underwent an intramolecular substitution, affording the desired thietanes 429 by loss of dimethyl sulfide and the rhodium catalyst. In this transformation dimethyl sulfide worked as a transient nucleophile and leaving group in the reaction system [23] (Scheme 96).

**Scheme 94:** Mechanism for synthesis of thietanes 425 from thiiranes 419 and trimethyloxosulfonium iodide 424.

4.1.4 Synthesis via thermal expansion reaction of spirooxa-zoline-thiiranes:

Acyl isothiocyanates (RCONCS, 437) reacted with two equivalents of diphenyldiazomethane (438) at room temperature to give 4,5-dihydro-1,3-oxazole-4-spiro-2'-thiiranes 439, which isomerized thermally to 3-iminothietanes 440 [133-135] (Scheme 97).

4.2 Synthesis via ring contraction reactions

4.2.1 Synthesis through the ring contraction of thiiranes:

Compared to the ring expansion reactions of thiiranes to thietanes, the ring contraction of thiiranes to thietanes was applied in only limited cases. As an example, 3-chloro-2-
Scheme 95: Synthesis of functionalized thietanes from thiiranes and dimethylsulfonium acylmethylides.

Scheme 96: Mechanism for the rhodium-catalyzed synthesis of functionalized thietanes 429 from thiiranes 419 and dimethylsulfonium acylmethylides.

methylthiolane (441) underwent a ring contraction to give 2-(1-hydroxyethyl)thietane (442) and 2-(1-acetoxyethyl)thietane (443), respectively, when it was treated with water in ethanol or sodium acetate in acetic acid. The ring contraction proceeded through a thiiranium intermediate 444, which was isolated as chloride salt from the reaction system, indicating that an intramolecular nucleophilic substitution occurred, followed by the nucleophilic ring opening of the thiiranium ring [32] (Scheme 98).

Scheme 98: Synthesis of thietanes 443 from 3-chloro-2-methylthiolane (441) through ring contraction.

Scheme 97: Synthesis of 3-iminothietanes 440 through thermal isomerization from 4,5-dihydro-1,3-oxazole-4-spiro-2'-thiranes 439.
The ring contraction of thiolanes to thietanes was also utilized in the synthesis of thietanoses. The ring contraction was realized by the DAST-mediated conversion of thiofuranose 445 derived from D-xylose into the protected fluorinated thietanose 447 through a thiiranium intermediate 446 [135,136] (Scheme 99).

The similar DAST-mediated ring contraction of thiopentose 448 to thiotetraose 447 was also reported [20] (Scheme 100).

The DAST-mediated ring contraction of a thiopentose to a thiotetraose was realized in the direct conversion of the thiopentose in thionucleoside 450 to its thiotetraose analogue 451 [20] (Scheme 101).

The reaction of 3,3,5,5-tetramethylthiolane-2,4-dithione (452) with benzyne (453) gave a spirothietane-benzodithiole 456 in a good yield. In the transformation, the thiocarbonyl group of the dithioester in thiolane-2,4-dithione 452 initially attacked benzyne (453) to afford a betaine 454, which finally rearranged to give the spirothietane-benzodithiole 456 [137] (Scheme 102).

4.2.2 Synthesis via the ring contraction of 2H,6H-thiin-3-ones: 2H,6H-Thiin-3-ones 459 were first generated from 3-bromo-3-methylbutan-2-one (457) and mercapto esters (R₂C(SH)CO₂Et, 458) in four steps. Upon UV irradiation (350 nm) in either MeCN, benzene or Me₂CHOH solution, these newly synthesized heterocycles 459 isomerized efficiently to 2-(1-alkenyl)thietan-3-ones 461. The rearrangement was assumed to proceed via an excited-singlet state and sulfuranyl-alkyl biradicals 460 formed by bonding of C(α) of the enone C=C bond on sulfur as possible intermediates [21] (Scheme 103).
5. Phosphorothioate-mediated synthesis

5.1. Synthesis from enones

In 1981, Ueno and co-workers were the first who utilized O,O-diethyl hydrogen phosphorodithioate (462) as a nucleophile in the Michael addition of chalcones 462, affording O,O-diethyl S-(1,3-diaryl-3-oxopropyl)phosphorodithioates 464, which were further reduced with sodium borohydride and treated with sodium hydride to give rise to 2,4-diarylthietanes 465 [138] (Scheme 104).

In this reaction, the O,O-diethyl S-(1,3-diaryl-3-oxopropyl)phosphorodithioates 464 were converted to the corresponding alkoxides 467 after the reduction with sodium borohydride and the treatment with sodium hydride. The alkoxides 467 underwent an intramolecular nucleophilic addition to the phosphorus atom followed by an elimination and an intramolecular substitution to give rise to 2,4-diarylthietanes 465. In this strategy, O,O-diethyl hydrogen phosphorodithioate (463) first worked as a nucleophile to introduce a sulfur atom in the substrates followed by its conversion to O,O,O-trialkylphosphorothioate 469 as a leaving group in the final nucleophilic substitution [138] (Scheme 105).

In 2002, when Yadav worked independently, he further developed Ueno’s synthetic strategy. He and his co-worker treated O,O-diethyl S-(1,3-diaryl-3-oxopropyl)phosphorodithioates 464.
with nucleophiles, such as cyanide, methanethiolate, and ethanethiolate, in the solid state under microwave irradiation affording the 2-functionalized 2,4-diarylthietanes 470 [139] (Scheme 106).

In this reaction, the nucleophiles attacked the carbonyl group of O,O-diethyl S-(1,3-diaryl-3-oxopropyl)phosphorodithioates 464 to generate the corresponding alkoxides 471. Compounds 471 then underwent an intramolecular nucleophilic addition to phosphorus followed by an elimination and an intramolecular substitution to give rise to 2-functionalized 2,4-diarylthietanes 470 [139] (Scheme 107).

In 2011, Myrboth and co-workers mentioned a similar transformation. The reaction of O,O-diethyl hydrogen phosphorodithioate (463) and α,β-alkenones 474 was applied for the synthesis of 2,4-disubstituted thietanes 475 under microwave conditions. In this reaction, the nucleophile-induced cyclization of the Michael adducts in the presence of O,O-diethyl hydrogen phosphorodithioate (463) was realized in an alumina bath [140] (Scheme 108).

5.2. Synthesis from electron-deficient olefins

Yadav and co-worker first realized the synthesis of functionalized thietanes 478 from O,O-diethyl hydrogen phosphorodithioate (463), aromatic aldehydes 476, and electron-deficient olefins (acrylonitrile (187b) and methyl acrylate (187c)). They first conducted a Baylis–Hillman reaction to prepare the Baylis–Hillman adducts 477 of aromatic aldehydes 476 with acrylonitrile (187b) and methyl acrylate (187c), and then cyclized the adducts 477 with O,O-diethyl hydrogen phosphorodithioate (463) in the presence of two equivalents of sodium hydride to afford the functionalized thietanes 478 [141] (Scheme 109).
To make the strategy more efficient, the same group developed a one-pot protocol. The one-pot three-component coupling reaction of \( \text{O,O-diethyl hydrogen phosphorodithioate (463)} \), aromatic aldehydes \( 476 \), and electron-deficient olefins \( 187b,c \) proved as efficient method for the highly diastereoselective synthesis of functionalized thietanes \( 478 \) in high yields [141] (Scheme 110).

Mechanistically, the reaction started with the Michael addition of phosphorodithioate \( (479) \) and acrylonitrile/acrylate \( (187b/187c) \) to generate the resonance-stabilized carbanions \( 480 \). The latter attacked aldehydes \( 476 \) to give the alkoxide anions \( 481 \) that underwent an intramolecular addition and elimination to generate thiolates \( 483 \). The thiolates then afforded the desired thietane products \( 478 \) after intramolecular substitution [141] (Scheme 111).

In 2012, Yadav and co-worker reported the synthesis of 3-nitrothietanes \( 486 \) from the Baylis–Hillman adducts \( 485 \) of nitroolefins and \( \text{O,O-diethyl hydrogen phosphorodithioate (463)} \). The reaction of \( \text{O,O-diethyl hydrogen phosphorodithioate (463)} \) and 3-aryl-2-nitropropenols \( 485 \) gave rise to trans-2-aryl-3-nitrothietanes \( 486 \) in the presence of sodium hydride [142] (Scheme 112).

The Baylis–Hillman alcohols \( 485 \) could also be oxidized to 3-aryl-2-nitropropenals \( 487 \) with IBX as an oxidant. They were then converted to 2,3,4-trisubstituted thietanes \( 488 \) after the treatment with \( \text{O,O-diethyl hydrogen phosphorodithioate (463)} \) followed by \( \text{[bmim][X-Y]} \) in the presence of sodium hydride [142] (Scheme 112).

For the formation mechanism, \( \text{O,O-diethyl phosphorodithioate (479)} \) nucleophilically attacked the 3-aryl-2-nitropropenals \( 485 \) to generate alkoxides \( 489 \), which underwent an intramolecular addition and elimination followed by an intramolecular substi-
tution to afford trans-2-aryl-3-nitrothietanes 486 as the product [142] (Scheme 113).

Wu and Robertson realized the first asymmetric synthesis of (S)-2-phenylthietane (497) through a similar phosphorothioate-mediated strategy. They first prepared O,O-diethyl S-(3-oxo-3-phenylpropyl) phosphorothioate (494) from 3-iodo-1-phenylpropan-1-one (492) and sodium O,O-diethyl phosphorothioate (493). After an asymmetric borane reduction and the treatment with sodium hydride, (S)-2-phenylthietane (497) was obtained in 74% yield with 87% ee via the similar cyclization step [143] (Scheme 114).

In 2016, Soós and co-workers developed a bifunctional thio-urea-catalyzed stereoablative retro-sulfa-Michael reaction of S-(1,3-diaryl-3-oxopropyl) O,O-diethyl phosphorothioates 498 under biphasic conditions, that afforded enantiomerically enriched S-(1,3-diaryl-3-oxopropyl) O,O-diethyl phosphorothioates 499. Both enantiomeric products (R)- and (S)-499 were obtained in up to 40% yield with up to 90% ee in the presence of different enantiomeric catalysts, cat 1 and cat 2. After the asymmetric borane reduction under the catalysis of one of a pair of enantiomeric catalysts (cat 3 and cat ent-3) and the treatment with sodium hydride, all of four enantiomerically enriched 2,4-diarylthietanes 501 were obtained with up to 99% ee [143] (Scheme 115).

6. Synthesis via cyclizations
6.1 Synthesis via intramolecular thioesterification
2-Amino-3-mercapto-3-methylbutanoic acid (502), penicilamine, was converted into the corresponding thietan-2-one derivative 503 with acetic anhydride as a coupling reagent in pyridine accompanied by N-acetylation [145] (Scheme 116).

Similarly, Pattenden and Shuker cyclized 3-mercapto-3-methylbutanoic acid into 4,4-dimethylthietan-2-one for the synthesis of antitumor antibiotic Leinamycin [146,147]. Leinamycin (LNM) is a new antitumor antibiotic produced by Streptomyces atroolivaceus S-140. For its preparation, its important fragment was first synthesized from butane-1,4-diol (504) as starting material. 3-Mercapto carboxylic acid 505 as a key intermediate was cyclized with isobutyl chloroformate as a coupling reagent, affording the thietan-2-one derivative 506 [147,148] (Scheme 117).

In 2013, Gates’s group prepared a small analogue of the anticancer natural product leinamycin. They first synthesized 3-mercapto carboxylic acid 510 as a key intermediate and then cyclized it with DCC and DMAP as coupling reagents, affording the thietan-2-one derivative 511 which was further converted into a small analogue 512 of leinamycin [149] (Scheme 118).

To investigate the structure–activity relationship of leinamycin (LNM), 8,4'-didehydroxy-leinamycin (515) was synthesized. During the synthesis, a spirothietan-2-one intermediate 514 was prepared through an intramolecular thioesterification of 3-mercaptopalcanoic acid 513 and further transformed into the target product 515 [150] (Scheme 119).

Tetrahydrolipstatin (orlistat) is currently marketed as xenical for the treatment of obesity [151]. Crich and co-workers synthe-

![Scheme 113: Mechanism on the phosphorodithioate-mediated synthesis of 1,2-disubstituted thietanes (±)-486.](image-url)

![Scheme 114: Asymmetric synthesis of (S)-2-phenylthietane (497).](image-url)
Scheme 115: Asymmetric synthesis of optically active 2,4-diarylthietanes.

Scheme 116: Synthesis of 3-acetamidothietan-2-one 503 via the intramolecular thioesterification of 3-mercaptoalkanoic acid 502.

 sized its sulfur analogue 518 from (S)-(−)-epichlorohydrin ((S)-142a). After 12 steps, 3-mercapto carboxylic acid 516 was obtained and further cyclized into a thia-β-lactone 517 in more than 65% yield with EDCI as a coupling reagent and pentafluorophenyl ester as an active ester intermediate. After 3 steps, the thia-β-lactone 517 was transformed into thiatetrahydrolipstatin 518 [152] (Scheme 120).
Scheme 117: Synthesis of 4-substituted thietan-2-one via the intramolecular thioesterification of 3-mercaptoalkanoic acid.

Scheme 118: Synthesis of 4,4-disubstituted thietan-2-one 511 via the intramolecular thioesterification of the 3-mercaptoalkanoic acid 510.

Scheme 119: Synthesis of a spirothietan-2-one 514 via the intramolecular thioesterification of 3-mercaptoalkanoic acid.

Scheme 120: Synthesis of thiatetrahydrolipstatin starting from (S)-(-)-epichlorohydrin ((S)-142a).
6.2 Synthesis via the intramolecular nucleophilic substitution of 2-bromoalk-1-ene-4-thiols

When Narasaka and co-workers investigated the formal intramolecular nucleophilic substitution at $sp^2$ carbon centers for the preparation of oxygen, nitrogen, and sulfur-containing unsaturated five-membered heterocycles, they found that the method could be applied for the synthesis of 2-alkylidenethietanes. They obtained 2-phenethyl-4-(propan-2-ylidene)thietane (520) from 5-bromo-6-methyl-1-phenylhept-5-ene-3-thiol (519) as a substrate in 1,3-dimethyl-2-imidazolidinone (DMI) as solvent [25] (Scheme 121).

They further applied the method to synthesize 2-phenethyl-4-(propan-2-ylidene)thietane (520) from $S$-(5-bromo-6-methyl-1-phenylhept-5-en-3-yl)thioacetate (521) directly because $K_2CO_3$ led to deacetylation of the acetyl group from the thioacetate 521, which was prepared from the corresponding alcohol and thiolaetic acid with the Mitsunobu reagent [153] (Scheme 122).

The method was applied using various substrates to synthesize a series of 2-alkylidenethietanes 528–532. The $S$-(2,7-dibromo-octa-1,7-dien-4-yl)thioacetate (527) generated the 2-methylidenethietane derivative 532 exclusively under the reaction conditions, revealing that the reaction preferred the 4-exo ring closure [153,154] (Scheme 123).
In 2009, Li and his co-workers developed a ligand-free CuI-catalyzed intramolecular S-vinylation of 2-bromo/chloroalk-1-ene-4-thiols 533–539 for the preparation of 2-alkylidenethietanes 528, 532, and 540–544. They designed some substrates 537–539 possessing double bromovinyl moieties with different chain lengths and performed the reaction. The results indicated that the reaction preferred the 4-exo ring closure over other modes, such as 5-exo, 6-exo, and 6-endo cyclizations [155] (Scheme 124).

6.3 Synthesis via nucleophilic addition

The reaction of bulky α,β-unsaturated trifluoromethyl ketone, adamantylmethylenetrifluoromethyl ketone (545), and ammonium hydrosulfide generated a spiroadamantine-thietan-3-ol 548 in 86% yield. The reaction involved a thia-Michael addition, proton transfer, and nucleophilic addition [156] (Scheme 125).

The de novo synthesis of the enantiopure thietane derivative 553, a four-membered ring thiosugar, was conducted from cis-but-2-ene-1,4-diol (47). The two asymmetric centers were...
generated first via the Sharpless asymmetric epoxidation. The epoxide 549 was then converted into the corresponding thirane 550 through a cyclic xanthate intermediate generated by the treatment with CS₂ and KH. After the protection of the secondary hydroxy group, methanolation of the xanthate afforded the desired thirane 550 in 63% overall yield. The AgOAc-mediated regioselective ring opening of the thirane 550 provided a thiol 551, which was converted to 1-O-ethyl-thietanoside 553 through the acid-catalyzed elimination of EtOH followed by the thiol nucleophilic addition induced by the treatment with CSA in refluxing benzene. The highly stereoselective conversion proceeded via an oxocarbenium intermediate 552, leading to the thermodynamically favored trans,trans-substituted thietane derivative 553 [157] (Scheme 126).

(Z)-α-Silyl vinyl sulfides 554 were prepared from (Z)-α-silyl enethiols and chloromethyl ketones and further converted into 2-alkylidenethietan-3-ols 557 by the treatment with fluoride. The conversion included the desilylation, intramolecular nucleophilic addition, and protonation [158] (Scheme 127).

The treatment of propargylbenzene (558) with butyllithium generated 1,3-dilithiopropargylbenzene (559), which underwent a nucleophilic addition to isothiocyanates 560 followed by protonation, isomerization, intramolecular nucleophilic addition, and methylation, affording 2-iminothietane derivatives 564 [159,160] (Scheme 128).

One example of a 2-benzylidenethietane 567 was prepared in 82% yield from 1-phenylhex-1-en-4-ylthioacetate (565) via a nickel complex-catalyzed electroreduction [161] (Scheme 129). However, the electrochemical synthetic method was widely applied for the synthesis of thiacyclopentanes and thiacyclohexanes [161].
6.4 Synthesis via electrocyclic reaction
Besides the cyclization through the inter- and intramolecular nucleophilic substitutions, the photo-assisted electrocyclic reaction of \( N \)-monosubstituted \( \alpha,\beta \)-unsaturated thioamides 568 was also applied for the synthesis of 2-iminothietane derivatives 569 [162] (Scheme 130).

![Scheme 130: Synthesis of 2-iminothietanes 569 via the photo-assisted electrocyclic reaction of \( N \)-monosubstituted \( \alpha,\beta \)-unsaturated thioamides.]

6.5 Synthesis via nucleophilic addition–elimination
Iminothietanes [162-169], diiminothietanes [101,170], and trimiminothietanes [171] are less reported four-membered thia-heterocycles. Langer and Doring prepared ethyl 3,4-diiminothietane-2-carboxylates 573 through the cyclization of the vicinal dianion 571 generated from ethyl thioglycolate (570) and LDA in TMEDA with 1,2-dielectrophiles, bis(imidoyl chloride)s 572. However, only one target diiminothietane 572a was obtained in 40% yield (\( R = 4\text{-MeC}_6\text{H}_4 \)). The other two reacted directly with another molecule of the dianion 571 to generate 4-amino-5-imino-1,2-dithiole-3-carboxylates 574 [172] (Scheme 131).

![Scheme 131: Synthesis of 2-iminothietane-2-carboxylates from ethyl thioglycolate (570) and bis(imidoyl chloride)s.]

7 Miscellaneous syntheses
Press and co-workers developed a rearrangement method to derivatize aromatic azaheterocyclethiones, including 1,9-dihydro-6H-purine-6-thiones 575, 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4(3H)-thione (576), pyrimidine-4(3H)-thione (577), quinoline-2(1H)-thione (578), and pyridine-2(1H)-thione (579), into the corresponding \( N \)-thietan-3-yl-\( \alpha \)-oxo nitrogen-containing heterocycles 583–587 with chloromethylloxirane (142a) as an alkylation reagent. For the reaction process, the reaction of 1,9-dihydro-6H-purine-6-thione (575a) and chloromethylloxirane (142a) first generated the \( S \)-alkylated intermediate 580 in the presence of sodium bicarbonate. After the treatment with NaOH, the intermediate 580 converted into tricyclic intermediates 581 and 582, which finally produced the \( N \)-thietan-3-yl product 583a in more than 99% yield in methanolic sodium methoxide through a rearrangement [173] (Scheme 132).

Recently, the nickel-catalyzed reductive thiolation of unactivated alkyl bromides and thiosulfonates was developed to synthesize thioethers. The method could also be applied in the synthesis of thietane derivatives. Such as, thietan-3-yl benzoate (590) was prepared through the nickel-catalyzed intramolecular reductive thiolation of \( \beta -(3\text{-bromo-2-benzoyloxypropyl})\)benzenesulfonothioate (588) [174] (Scheme 133).

The thiophilic ring-opening reaction of 3,3-bis(trifluoromethyl)-5-butoxy-1,2-dithiolane (591) proceeded with the treatment of the nucleophile CF\(_3\)SiMe\(_3\) to generate 2,2-bis(trifluoromethyl)-4-butoxythietane (374d) as an intermediate. The latter compound further reacted with another molecule of CF\(_3\)SiMe\(_3\) to afford a mixture of 2,2-bis(trifluoromethyl)-4-butoxythietane (374d) and (1-butoxy-4,4-difluoro-3-(trifluoromethyl)but-3-en-1-yl)(trifluoromethyl)sulfane (592) in a ratio of 60:20 [175] (Scheme 134).
The reaction of enamine 593 and methanesulfonyl chloride in the presence of triethylamine generated 3-amino-2-propylthietane 1,1-dioxide 594. After the methylation with MeI and Hofmann elimination, 2-propyl-2H-thiete 1,1-dioxide (595) was obtained. Compound 595 was converted into 2-propylthietane (597) after hydrogenation and reduction [176] (Scheme 135).

It is well known that cyclobutane-1,3-dithiones undergo ring rearrangement and isomerization into thietane-2-thiones in the presence of bases [177,178]. 2,2,4,4-Tetramethylcyclobutane-1,3-dithione (598) generated 3,3-dimethyl-4-(propan-2-ylidene)thietane-2-thione (602) in the presence of triethylamine. It further reacted with the fluorinated nitrile imine 599 derived
from trifluoroacetaldehyde phenylhydrazonoyl bromide in the presence of triethylamine to give 1,8-dithia-5,6-diaza-
spiro[3.4]oct-6-ene 603, the spiro thietane-1,3,4-thiadiazolidine
derivative, through a [2 + 3] cycloaddition [179] (Scheme 136).

In 2006, a Russian group attempted to prepare thietane (605)
from 1-bromo-3-chloropropane (604) and sulfur in the presence
of hydrazine hydrate and KOH. The yield depended on the ratio
of KOH:S. When the ratio was 1:2, thietane (605) was obtained
in 26% yield, however, polymeric –(SCH₂CH₂S)ₙ– (607)
was the major product in 65% yield [180] (Scheme 137).

Conclusion
Thietanes are one class of important aliphatic four-membered
thiaheterocycles. They are not only crucial pharmaceutical cores

Scheme 133: Synthesis of thietan-3-yl benzoate (590) via the nickel-catalyzed intramolecular reductive thiolation of S-(3-bromo-2-benzoyloxypropyl) benzenesulfonothioate 588.

Scheme 134: Synthesis of 2,2-bis(trifluoromethyl)thietane from 3,3-
bis(trifluoromethyl)-1,2-dithiolane.

Scheme 135: Synthesis of thietanes from enamines and sulfonyl chlorides.

Scheme 136: Synthesis of spirothietane 603 via the [2 + 3] cycloaddi-
tion of 2,2,4,4-tetramethylcyclobutane-1,3-dithione and nitrile imine.

Scheme 137: Synthesis of thietane (605) from 1-bromo-3-chlo-
ropropane and sulfur.
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