Seven-Membered Rings With Three Heteroatoms 1,2,5

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Nomenclature

mCPBA *meta*-Chloroperoxybenzoic acid
DMAD Acetylene dicarboxylate
DGl Diglyme
MW Microwave irradiation
LR Lawesson's reagent
$TMSN_3$ Trimethylsilyl azide
PMB *para*-Methoxybenzyl
MS Molecular sieves
OBP Oligomeric benzyl phosphates

1 Introduction

This article covers seven-membered heterocyclic systems with three heteroatoms in 1st, 2nd, and 5th positions of the ring and their aryl/heteroaryl-fused derivatives. It reviews the literature from 2007 to early 2020 and continues the previous three editions of "Comprehensive Heterocyclic Chemistry".[1–3] The central part of the work is devoted to N-, O-, S-containing heterocycles. Condensed heterocycles discussed in this article are grouped into four sections:

Systems with three same-type heteroatoms and their aryl/heteroaryl-fused derivatives; sections:
2. 1,2,5-Triazepane;
3. 1,2,5-Trioxepane;
4. 1,2,5-Trithiepane;

Systems with two same-type heteroatoms plus one different type heteroatom and their aryl/heteroaryl-fused derivatives; sections:
5. 1,2,5-Oxadiazepane;
6. 1,4,5-Oxadiazepane;
7. 1,2,5-Thiadiazepane;
8. 1,4,5-Thiadiazepane;
9. 1,5,2-Dioxazepane;
10. 1,5,2-Dithiazepane;
11. 1,2,5-Dithiazepane;
12. 1,4,5-Oxadithiepane;

Systems containing N, O, S heteroatoms simultaneously and their aryl/heteroaryl-fused derivatives; sections:
13. 1,5,2-Oxathiazepane;
14. 1,4,5-Oxathiazepane;

Systems containing at least one not N, O, or S heteroatoms and their aryl/heteroaryl-fused derivatives; **Section 15**. Systems containing at least one not N, O, or S heteroatom;

No system with heteroatoms different from above has been reported in the reviewed period. The ring numbering for all considered fused heterocycles and their nomenclature are shown in **Table 1**.

Compounds given in patents without chemical properties or production are not part of this review. Synthesis, reactivity, and structural peculiarities, application, and representative compounds with exciting properties are discussed within each section.

2 1,2,5-Triazepane

Kharaneko et al. have synthesized 2,7-diphenyl-5,8-dihydro-4H-pyrazolo[5,1-d][1,2,5]triazepin-4-one **2** starting from 2,6-diphenyl-4H-pyrazolo[5,1-c][1,4]oxazin-4-one **1.**[4] The reaction of **1** with hydrazine hydrate in 2-ethoxyethanol under reflux during 4 h leads to the formation of 1,2,5-triazepane ring (**Scheme 1**). The yield of the target pyrazolo[5,1-d][1,2,5]triazepin-4-one **2** reached 97%. Heating of pyrazolotriazepinone **2** with 85% phosphoric acid at 140 °C for 1 h leads to outgoing of one nitrogen atom from the cycle and rearrangement of the seven-membered ring to 5-amino-2,6-diphenylpyrazolo[1,5-*a*]pyrazin-4(5H)-one **3** in 96% yield (**Scheme 1**).

Treatment of **2** with Lawesson's reagent in toluene for 2 h leads to corresponding 2,7-diphenyl-5,8-dihydro-4H-pyrazolo[5,1-d][1,2,5]triazepine-4-thione **4** in 60% yield (**Scheme 2**). The authors have investigated further transformations of thione **4** in detail.[4] The reaction of **4** with dimethyl sulfate in the presence of a base in acetone leads to the *S*-methylated product 4-(methylsulfanyl)-2,7-diphenyl-8H-pyrazolo[5,1-d][1,2,5]triazepine **5** in high yield (98%). Hydrazinolysis of **4** in 2-ethoxyethanol produces 4-hydrazinyl-2,7-diphenyl-8H-pyrazolo[5,1-d][1,2,5]triazepine **6** in 90% yield. Similarly, reaction with morpholine under reflux for 1 h gives 4-(morpholin-4-yl)-2,7-diphenyl-8H-pyrazolo[5,1-d][1,2,5]triazepine **7** as fine yellow crystals in 93% yield (**Scheme 2**).

The authors have found that hydrazinyl-substituted pyrazolotriazepine **6** is a diverse object for further synthetic modification.[1] Acylation of **6** with acetyl chloride or 4-methoxybenzoyl chloride in dioxane-hydrogen chloride solution under reflux for 2 h produces tricyclic

Table 1 Seven-membered rings with three heteroatoms 1,2,5 discussed in this review.

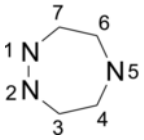
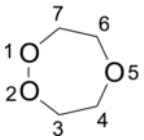
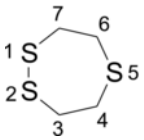
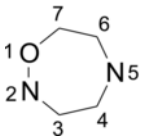
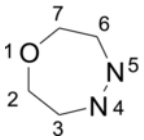
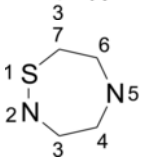
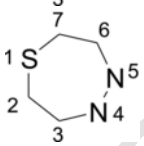
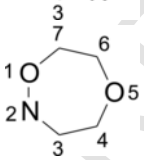
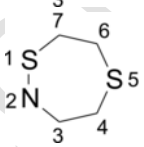
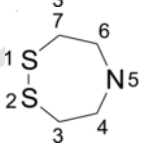
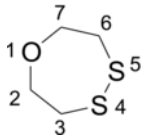
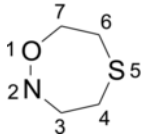
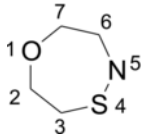
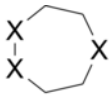
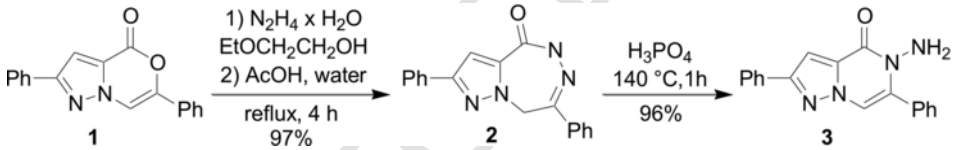
Fused system number (section)	*Ring System*	*Chemical abstract name of basic structure*
1 (**Section 2**)		1,2,5-Triazepane
2 (**Section 3**)		1,2,5-Trioxepane
3 (**Section 4**)		1,2,5-Trithiepane
4 (**Section 5**)		1,2,5-Oxadiazepane
5 (**Section 6**)		1,4,5-Oxadiazepane
6 (**Section 7**)		1,2,5-Thiadiazepane
7 (**Section 8**)		1,4,5-Thiadiazepane
8 (**Section 9**)		1,5,2-Dioxazepane
9 (**Section 10**)		1,5,2-Dithiazepane
10 (**Section 11**)		1,2,5-Dithiazepane

Table 1 (Continued)

Fused system number (section)	*Ring System*	*Chemical abstract name of basic structure*
11 (**Section 12**)		1,4,5-Oxadithiepane
12 (**Section 13**)		1,5,2-Oxathiazepane
13 (**Section 14**)		1,4,5-Oxathiazepane
14 (**Section 15**)	 where X ≠ C, and at least one of X ≠ N, O, S	Systems containing at least one not N, O, or S heteroatom



Scheme 1

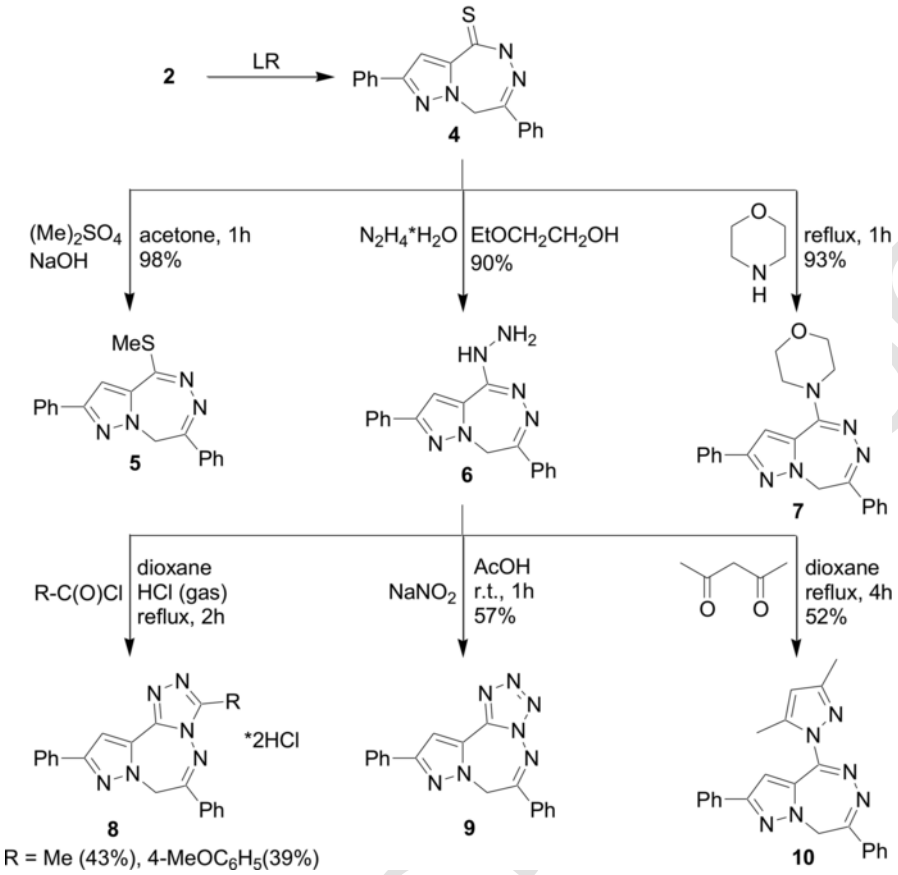
d]tetrazolo[1,5-b][1,2,5]triazepine **9** were obtained in 57% yield. Reflux of 1–6 with 2,4-pentandione-dioxane mixture leads to formation of 4-(3,5-dimethyl-1H-pyrazol-1-yl)-2,7-diphenyl-8H-pyrazolo[5,1-d][1,2,5]triazepine **10** as fine colorless crystals in 52% yield.

Oxazinone **11** produces 7-hydrazino-2-methyl-7-phenyl-5,6,7,8-tetrahydro-4H-pyrazolo[5,1-d][1,2,5]triazepin-4-one **12** when treated with hydrazine hydrate in methanol upon reflux for 3 h.[5] The yield of the hydrazinyl triazepine **12** equals 53%. Elimination of hydrazinyl group can be achieved via boiling of **12** in ethyl cellosolve for 1 h (**Scheme 3**). The target 2-methyl-7-phenyl-5,8-dihydro-4H-pyrazolo[5,1-d][1,2,5]triazepin-4-one **13** was obtained as fine colorless crystals in 84% yield.

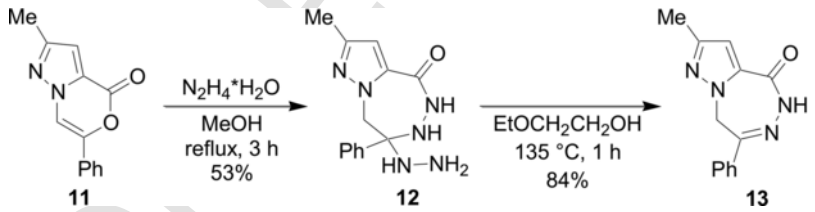
Kharaneko have synthesized 1,2,5-triazepin-4-one **15** from pyrrole **14** via the treatment with 4-toluenesulfonic acid in acetic acid in 97%yield.[6] Next, transformation to thio-analog **16** in 69% yield can be done via the action Lawesson's reagent in toluene under reflux. 7,8,9-Trimethyl-1-phenyl-5H-pyrrolo[2,1-d][1,2,5]triazepine-4-thiol **16** is a convenient object for further functionalization (**Scheme 4**). Thus, boiling of **16** in piperidine produces derivative **17** in 51% yield. Alkylation of acetone basic solution of **16** with methyl iodide gives 7,8,9-trimethyl-4-(methylsulfanyl)-1-phenyl-5Hpyrrolo[2,1-d][1,2,5]triazepine **18** in 62% yield. Methyl acrylate in the presence of catalytic quantity of sodium hydroxide transforms **16** into methyl 3-[(7,8,9-trimethyl-1-phenyl-5H-pyrrolo[2,1-d][1,2,5]triazepin-4-yl)sulfanyl]propanoate **19** in 65% yield.

Liu and *co*-authors have achieved a facile synthesis strategy for obtaining poly-substituted triazepinium salts that show excellent solid-state fluorescence properties.[7] Based on the crystal structure of the synthesized salts **21** and the DFT calculations, the authors claim that the fluorescence performance of salts **21** could be regulated by adjusting the dihedral angle between the triazepinium skeleton and the substituted fragment. Synthesis under optimal reaction conditions based on the reaction of 4-amino-3,5-di(4-pyridyl)-1,2,4-triazole with methyl ketones in the presence of iodine in DMSO (**Scheme 5**). The optimal reaction time of 10 h and a temperature of 80 °C give products in 60–90% yield.

El-Bordany and Alib have explored 2-[3-(3,4-dichlorophenyl)-3-oxoprop-1-enyl]-4H-benzo[3,1]oxazin-4-one **22** as a precursor to benzoxazinone, quinazolinone, and pyrazoloquinazolinone derivatives.[8] Authors have tested the cytotoxic activity of synthesized compounds against human breast cancer cells. The reaction of **22** with hydrazine hydrate in butanol under reflux for 4 h leads to the formation 3-amino-2-(3-(3,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinazolin-4(3H)-one **23**. Further reaction of **23** with



Scheme 2

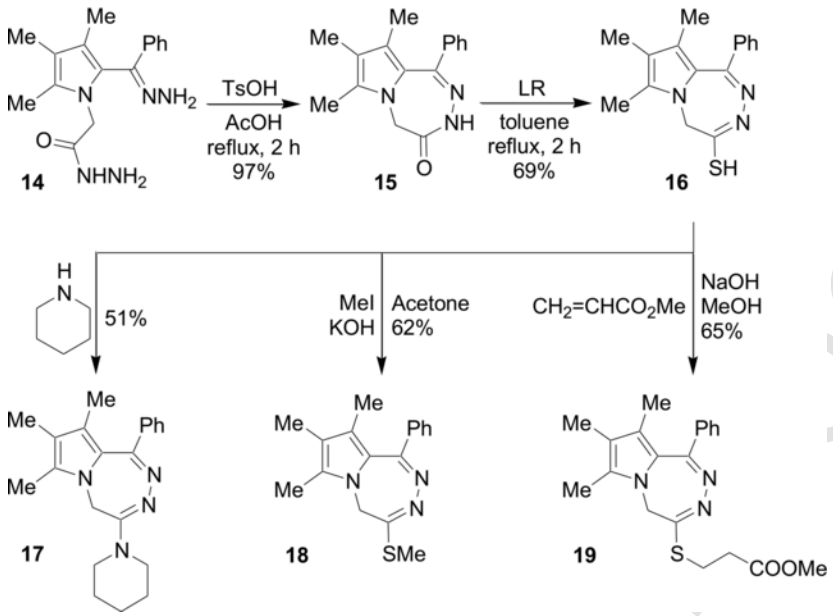


Scheme 3

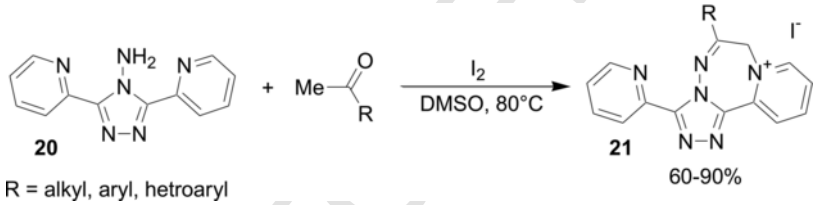
chloroacetonitrile in dimethylformamide under reflux for 6 h results in formation of white solid crystals of target 5-amino-2-(3,4-dichlorophenyl)-1,14b-dihydro-7H,9H-pyrazolo[10,50:5,6][1,2,5]triazepino[7,1-*b*]quinazolin-9-one **24** in 45% yield (**Scheme 6**).

Smejkal et al. have explored the herbicidal activity of aryldiones with 5-methoxy-1,2,5-triazepane ring.[9] Interaction of methoxyamine hydrochloride with oxirane in basic medium leads to *N*-methoxydiethnolamine **25** (**Scheme 7**). The next reaction with methansulfochloride leads to derivative **26**. Treatment of **26** with diBoc hydrazine in dimethylformamide in the presence of sodium hydride produces diBoc 1,2,5-triazepane derivative **27**, which under acid hydrolysis forms trihydrochloride salt of 5-methoxy-1,2,5-triazepane **28**. Under the action of N-carbethoxy-N′-Boc-hydrazine in dimethylformamide in basic conditions **26** forms 1,2,5-triazepane derivative **29**, which can be hydrolized by hydrogen chloride to 1-carbethoxy-5-methoxy-1,2,5-triazepane dihydrochloride **30**.

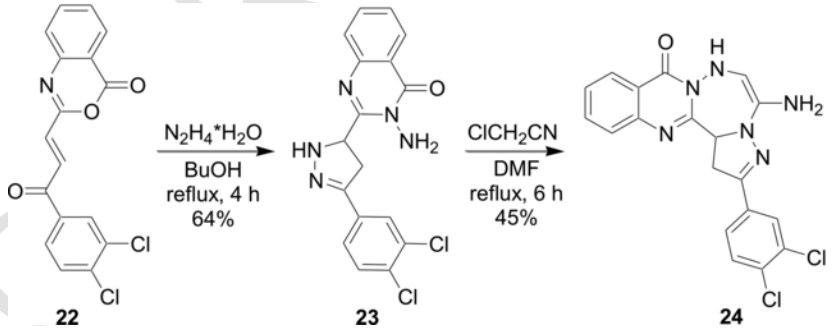
The authors have proposed two pathways to the target 2-aryl-cyclic-1,3-diones **32.**[9] Acylation of the derivative **30** in tetrahydrofuran in the presence of triethylamine as a base and a catalytic amount of 4-dimethylamino pyridine (DMAP) leads to compounds **31** (**Scheme 8**). Cyclization of **31** to the target diones **32** was achieved in DMF under the action of sodium methoxide. Alternatively, diones **32** can be synthesized via the reaction of the trihydrochloride salt of 5-methoxy-1,2,5-triazepane **28** with arylmalonic esters in xylene under reflux in the presence of triethylamine. Further reaction of **32** with ethyl chloroformate in tetrahydrofuran under the action of triethylamine and a catalytic quantity of DMAP leads to carbonates **33**. The authors highlighted that post-emergence herbicidal action against grass weeds could be controlled through the variation of the aryl substituents.



Scheme 4



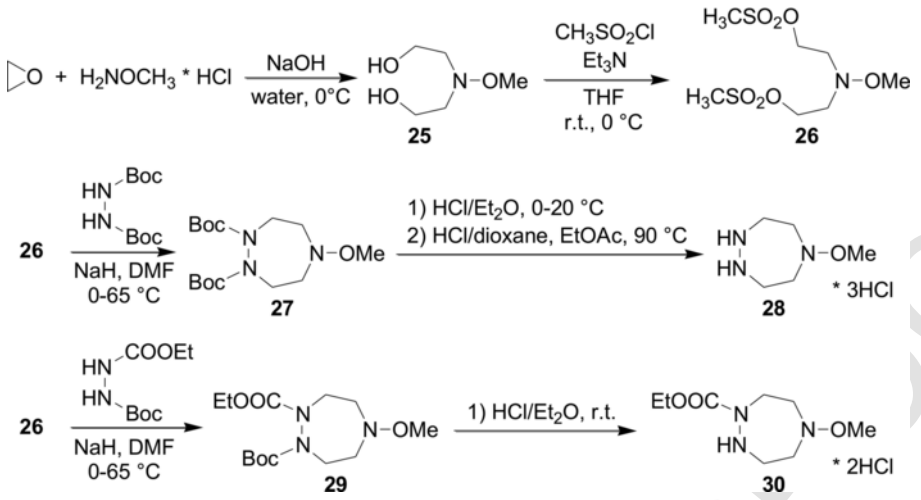
Scheme 5



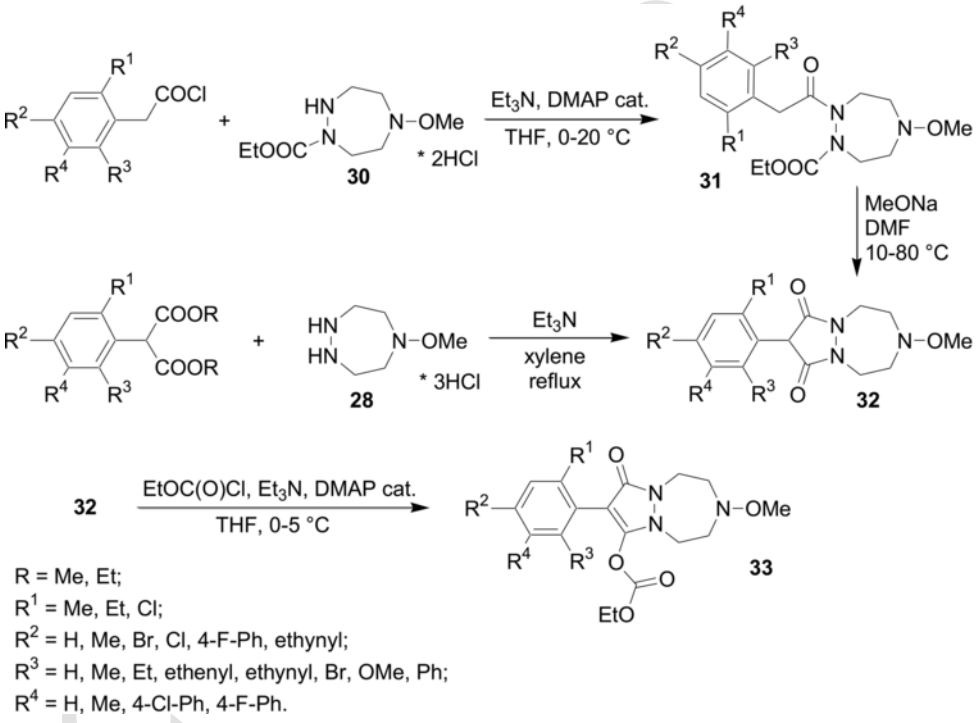
Scheme 6

Luescher et al. have developed a copper-promoted oxidative coupling of Sn-containing hydrazines with aldehydes to form chiral 1,4,5-oxadiazepanes and 1,2,5-triazepanes.[10] The formation of hydrazones **35** was performed using Sn-containing hydrazines **34** and corresponding aromatic aldehydes in dichloromethane under the action of 4 Å molecular sieves (**Scheme 9**). The cyclization to the target Boc-protected 2-aryl-5a,6,7,8-tetrahydro-3H-pyrrolo[1,2-b][1,2,5]triazepine-4(5H)-carboxylates **36** runs under the action of Cu(II) triflate and 2,6-lutidine. The reaction was taken in dichloroethane (EDC) at 65 °C for 16 h.

Földesi et al. have presented new tricyclic ring systems **38** based on the pyrrolotriazepine core.[11] The new structures have been synthesized via cycloaddition reactions of 1-arylpyrrolotriazepinones **37** (see **Scheme 10**) with nitrile oxides generated in situ from *N*-



Scheme 7

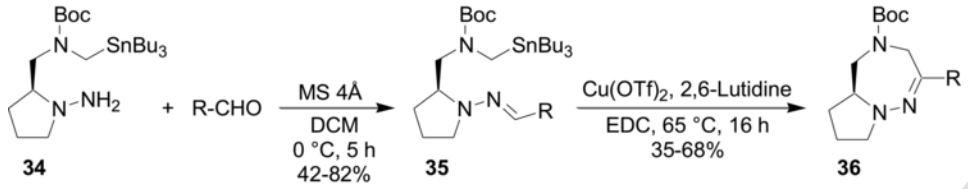


Scheme 8

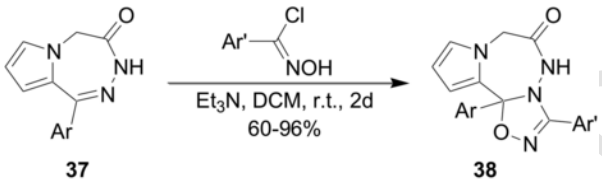
hydroxyarylcarboximidoyl chlorides with triethylamine. The reaction was performed in dichloromethane at room temperature for 2 days, giving the target compounds in high yields.

Similarly, systems **40** and **41** have been obtained by Földesi and co-authors via non-regioselective cycloaddition of 1,4-diarylpyrrolotriazepines **39** with nitrile oxides generated in situ from *N*-hydroxyarylcarboximidoyl chlorides (see **Scheme 11**). Dichloromethane was selected as a solvent, and triethylamine was used as a base. Taking reaction for 2 days at room temperature produces a mixture of products in high total yield. Flash chromatography or preparative TLC have been used for the separation of **40** and **41**.

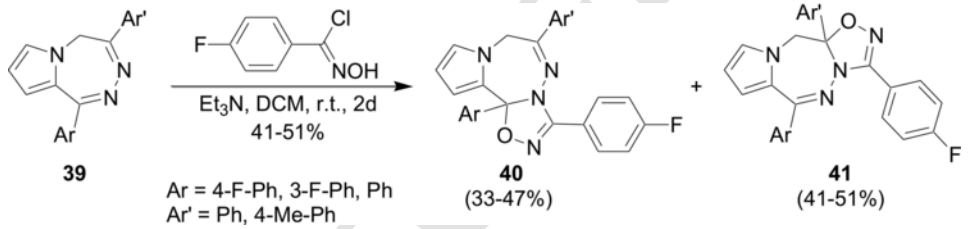
Wang et al. have described the use of Ugi tetrazole reaction of N-Boc protected hydrazine with α-amino acid-derived isocyanides, ketone, and trimethylsilyl azide.[12] The products' post cyclizations under acidic conditions in a one-pot fashion give cyclic products with tetrazolotriazepinone **42** and tetrazolopyrazinone **43** cores (**Scheme 12**).



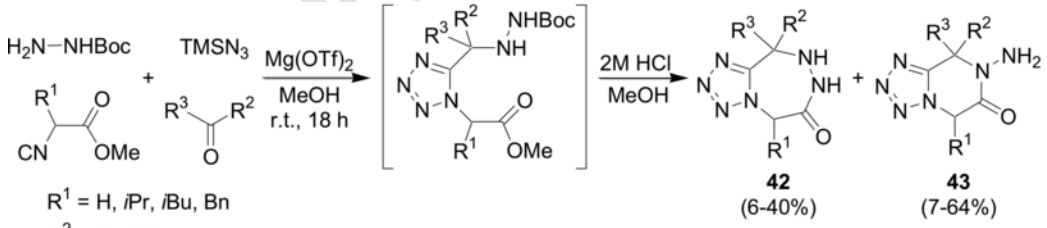
Scheme 9



Scheme 10



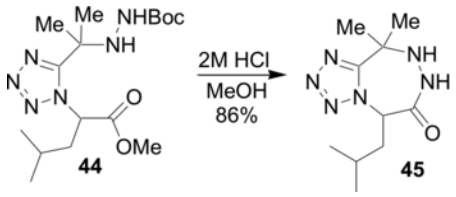
Scheme 11



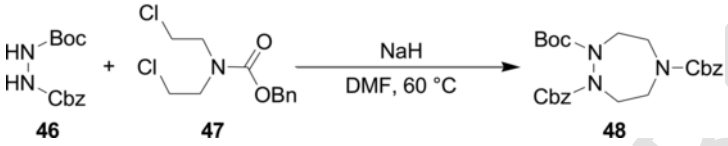
Scheme 12

N-Boc-protected hydrazine can be utilized in the Ugi tetrazole reaction to access a library of highly substituted 5-(hydrazinomethyl)-1-methyl-1H-tetrazoles **44.**[13] One of such type reagent was cyclized to access the interesting tetrazolotriazepine **45** in 86% yield (**Scheme 13**).

Suzuki et al. have developed a synthesis of [1,2,5]triazepane as a versatile structural unit for drug discovery.[14] Synthesis of the seven-membered core **48** based on the interaction of hydrazine **46** with bis(2-chloroethyl)carbamic acid benzyl ester **47** in DMF medium at 60 °C (**Scheme 14**).



Scheme 13



Scheme 14

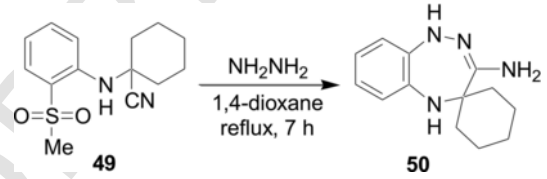
Synthesis of spiro[cyclohexanyl-1′-2-(3-amino)(1-H,5H)-1,4,5-benzotriazepine] **50** was described in the work of Soliman et al.[15] A mixture of compound **49** and hydrazine was refluxed in dioxane for 7 h (**Scheme 15**).

One-pot synthesis of fused 4,5-bridged 1,2,5-triazepine-3,6-diones **52** was developed by Neogi et al.[16] The last stage includes the cyclization of substituted proline methyl esters **51** under the action of hydrochloric acid (**Scheme 16**).

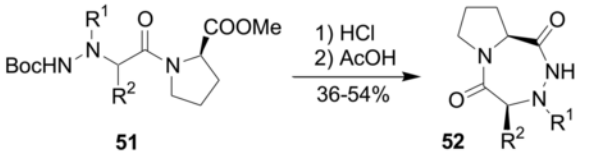
Milen et al. have disclosed a practical synthesis of 1-aryl-3H-pyrrolo[2,1-d][1,2,5]triazepin-4(5H)-ones and have used these as the starting materials for the synthesis of three new ring systems.[17] 2-(2-Aroylpyrrol-1-yl)acyl hydrazides **53** undergo acidic-ethanolic ring closure to produce target compounds **54** (**Scheme 17**).

A one-pot three-step technique for the conversion of oxazolino-2H-indazoles **55** into triazolotriazepinoindazolones **56** has been developed.[18] Propargyl bromide-initiated ring-opening of the oxazolino-2H-indazole followed by an azide-alkyne 1,3-dipolar cycloaddition to form the target compounds **56** in high yield (**Scheme 18**).

Suzuki et al. have synthesized a series of oxazolidinone analogs bearing a *N*-hydroxyacetyl-substituted [1,2,5]triazepanes **57** and **58** as homologs of an earlier drug candidate eperezolid (**Scheme 19**). High in vitro antibacterial activity against Gram-positive and Gram-negative linezolid-resistant pathogens was determined for several of these compounds.[19,20]



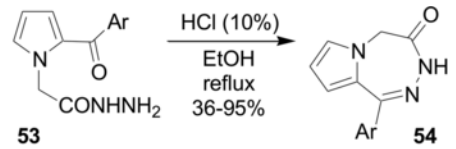
Scheme 15



R^1 = Bn, $CyCH_2$, $MeOOCCH_2$, Ph, 2-Me-Ph, 4-F-Ph

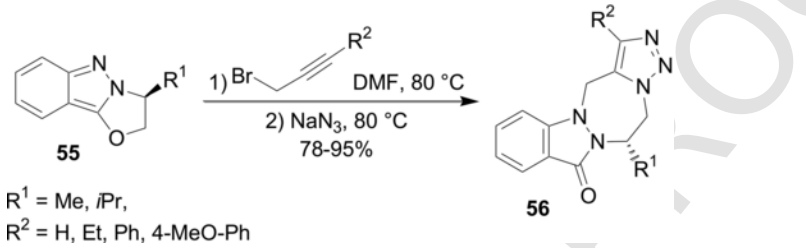
R^2 = Ph, 4-MeO-Ph, 4-MeS-Ph, 3,4-$(MeO)_2$-Ph, benzotiazol-2-yl, 1-naphthyl, 3-MeO-Ph, 3,4-(OCH_2O)-Ph, 3-F-4-MeO-Ph

Scheme 16



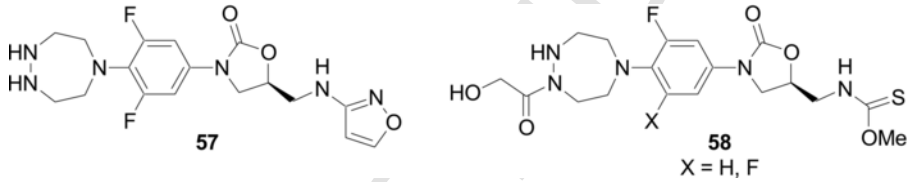
Ar = 4-F-Ph, 4-Cl-Ph, 3-F-Ph, 4-O_2N-Ph

Scheme 17



R^1 = Me, *i*Pr,
R^2 = H, Et, Ph, 4-MeO-Ph

Scheme 18



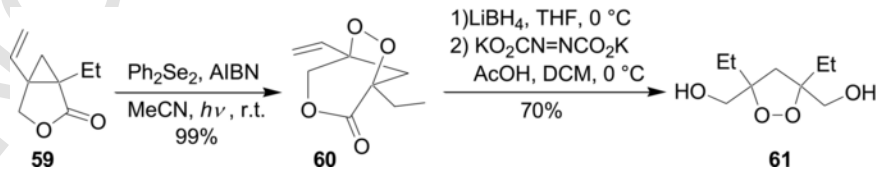
X = H, F

Scheme 19

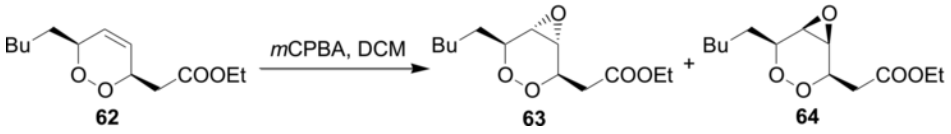
3 1,2,5-Trioxepane

Total synthesis of Plakortide E was proposed in the work of Sun et al.[21] One of the discussed multi-step route stages includes substance **60** with 1,2,5-trioxepane core (**Scheme 20**). The reaction of **59** with diphenyl diselenide and azobisisobutyronitrile in acetonitrile at room temperature under light irradiation leads to **60** in excellent yield. Reduction of **60** and the next reaction with potassium azodicarboxylate leads to **61**.

Fattorusso, with colleagues, have searched for new antimalarial agents.[22] Compound **62** dissolved in dichloromethane was treated with *meta*-chloroperbenzoic acid (**Scheme 21**). Reversed-phase HPLC purification yields compound **63** and **64** in 50% and 13% yield, respectively.



Scheme 20



Scheme 21

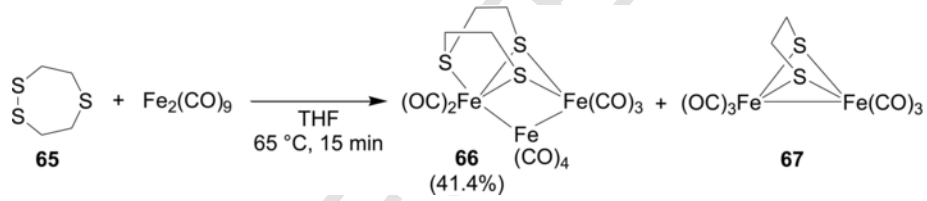
4 1,2,5-Trithiepane

Windhager et al. have investigated the interaction of 1,2,5-trithiepane **65** with nonacarbonyldiiron.[23] The reaction was carried out in tetrahydrofurane at 65 °C for 15 min. Products **66** and **67** were isolated (**Scheme 22**).

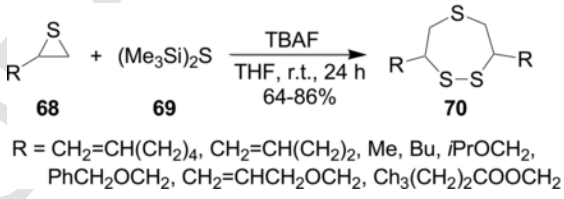
The reaction of substituted thiiranes **68** with bis(trimethylsilyl) sulfide **69** different leads to 3,7-disubstituted-1,2,5-trithiepanes **70.**[24] The synthesis was performed in tetrahydrofurane at room temperature under the action of tetrabutylammonium fluoride (TBAF) catalysis (**Scheme 23**).

5 1,2,5-Oxadiazepane

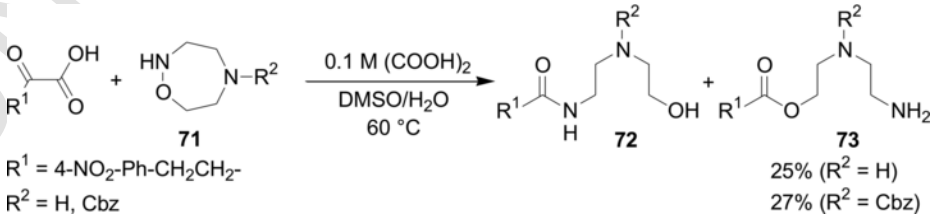
Rohrbacher and co-authors have explored a regioselective formation of ester versus amide during the reaction of cyclic hydroxylamines **71** with α-ketoacids.[25] In the case of non-protected hydroxylamine **71** (R^2 = H), the ester/amide ratio was determined as 71:29, and the ester **73** was isolated in 25% yield. Whereas in the case of benzyl carbamate protected hydroxylamine **71** (R^2 = Cbz) the ester/amide ratio equals 73:27, and the ester **73** was isolated in 27% yield (**Scheme 24**).



Scheme 22



Scheme 23



Scheme 24

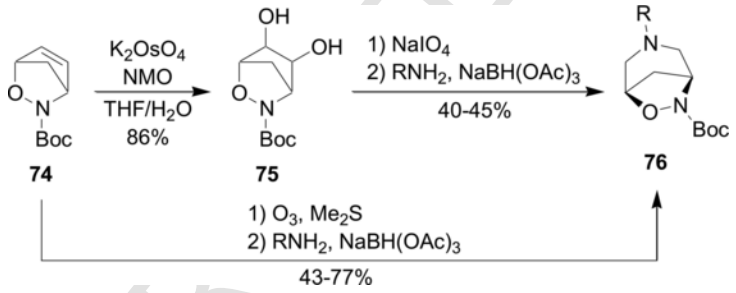
N-Substituted cis-5-amino-3-hydroxypiperidines can be obtained by a sequence of oxidative cleavage/reductive amination/reductive cleavage.[26] Authors developed a new straightforward route to drug-relevant scaffolds or fragments. Treatment of *tert*-butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **74** with *N*-methylmorpholine N-oxide and catalytic amount of potassium osmate leads to *tert*-butyl 5,6-dihydroxy-2-oxa-3-azabicyclo[2.2.1]heptane-3-carboxylate **75** (**Scheme 25**). Then, oxidation of **75** with sodium periodate and further reaction with a primary amine in the presence of sodium triacetoxyborohydride leads to the desired product **76**. Alternatively, ozonation of **74** in DCM − 78 °C and next reaction with a primary amine in DCM followed by addition of $NaBH(OAc)_3$ can be used for obtaining of target **76** in better yields.

Suzuki et al. have developed synthesis of [1,2,5]oxadiazepane as a versatile structural unit for drug discovery.[14] Synthesis of the seven-membered core **78** based on interaction of Boc-protected hydroxylamine **77** with bis(2-chloroethyl)carbamic acid benzyl ester in the presence of sodium hydride in dimethylformamide at 60 °C (**Scheme 26**).

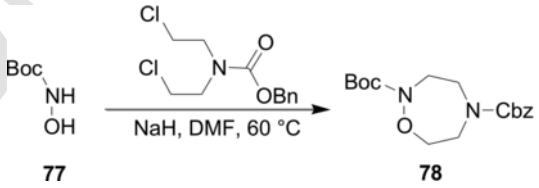
Suzuki et al. have synthesized a series of oxazolidinone analogs bearing *N*-hydroxyacetyl-substituted [1,2,5]oxadiazepanes **79** and **80** as homologs of an earlier drug candidate eperezolid (**Scheme 27**). High in vitro antibacterial activity against Gram-positive and Gram-negative linezolid-resistant pathogens was determined for several of these compounds.[19,20]

6 1,4,5-Oxadiazepane

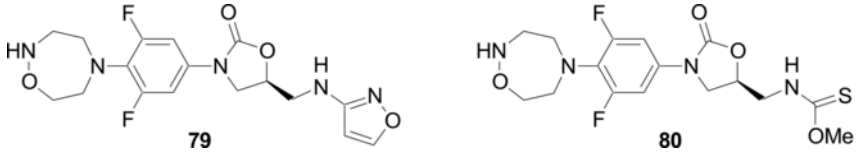
Chandrasekhar et al. have proposed a novel process for the preparation of key intermediate of pinoxaden and have patented their discovery.[27] The reaction is taken with nitrogen purging, under constant stirring with thermostat control of heating/cooling rates. The interaction of diethyl (2,6-diethyl 4-methyl phenyl) malonate **81** with 1,4,5-oxadiazepane dihydrochloride **82** was performed in xylene medium at room temperature (see **Scheme 28**). Then triethylamine was added, and the mixture was heated at reflux temperature for 6 h. After cooling, the precipitate of triethylamine hydrochloride was filtered off. After removing the solvent and purification of the target 8-(2,6-diethyl 4-methyl phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione **83,** the authors obtained 98% pure product in 90% yield.



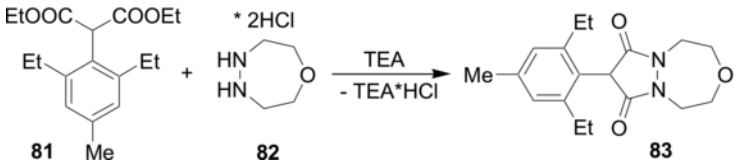
Scheme 25



Scheme 26



Scheme 27

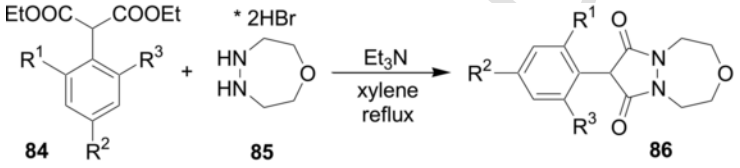


Scheme 28

Aseries of similar 1,4,5-oxadiazepane derivatives have been obtained in the work of Muehlebach et al.[28] The synthesis of aryldiones **86** basedon the interaction of substituted arylmalonic acids **84** with 1,4,5-oxadiazepane dihydrobromide **85** in xylene under reflux conditions (**Scheme 29**).

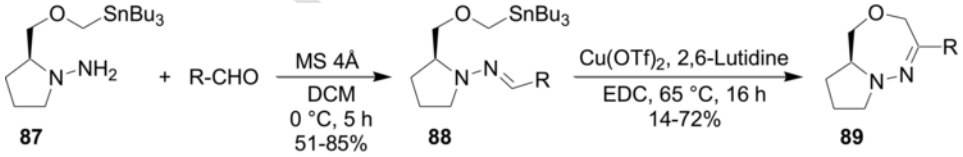
Luescher et al. have developed a copper-promoted oxidative coupling of Sn-containing hydrazines with aldehydes to form chiral 1,4,5-oxadiazepanes and 1,2,5-triazepanes.[10] The formation of hydrazones **88** was performed using Sn-containing hydrazines **87** and corresponding aromatic aldehydes in dichloromethane under the action of 4 Å molecular sieves (**Scheme 30**). The cyclization to 5a,6,7,8-tetrahydro-2-(thiophen-3-yl)-3*H*,5*H*-pyrrolo[2,1-c][1,4,5]oxadiazepines **89** takes place under the action of Cu(II) triflate and 2,6-lutidine in dichloroethane (EDC). Heating of the reaction mixture at 65 °C for 16 h produces the target compounds in 14–72%.

Mizuta et al. have described a method for synthetic routes to multi-functionalized-α-trifluoromethyl α,β-unsaturated lactones, and trifluoromethyl pyrazolinones.[29] Reaction of 3,3-dibromo-2-trifluoromethyl acrylic acid ethyl ester **90** with 1,4,5-oxadiazepane dihydrobromide **91** in dioxane under heating at 100 °C for 12 h leads to the target compound **92** in 83% yield (**Scheme 31**).



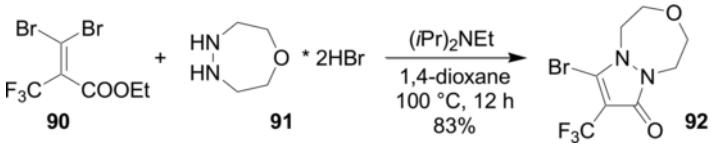
R^1 = Br, Me, Et, Pr, ethynyl,
R^2 = Me, Et, H, I, Ph,
R^3 = Br, Me, Et, Pr, *i*Pr, Cpr, ethynyl, 2-propynyl, MeO

Scheme 29



R = 2-Cl-4-F-Ph, 3-Br-Ph, 4-AcNH-Ph, 2-MeO-Ph, 4-MeO-Ph, 2-Me-Ph, -CH=CH-Ph, $-CH_2-CH_2-Ph$, 4-CF_3-Ph, 4-NO_2-Ph, 4-MeOOC-Ph, 4-CN-Ph, 3-pyridyl, 5-Me-1,2-oxadiazolyl, 3-furyl, 3-thiazolyl

Scheme 30



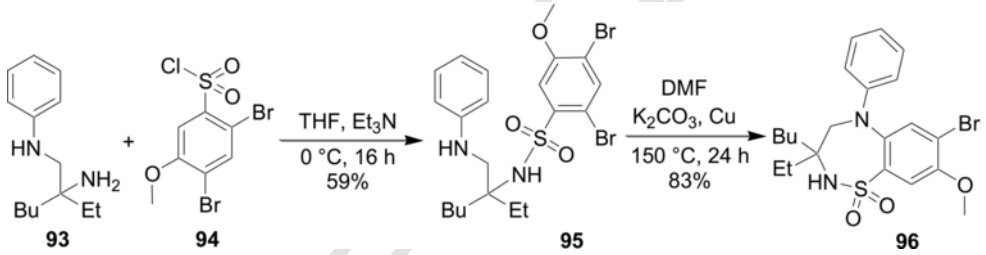
Scheme 31

7 1,2,5-Thiadiazepane

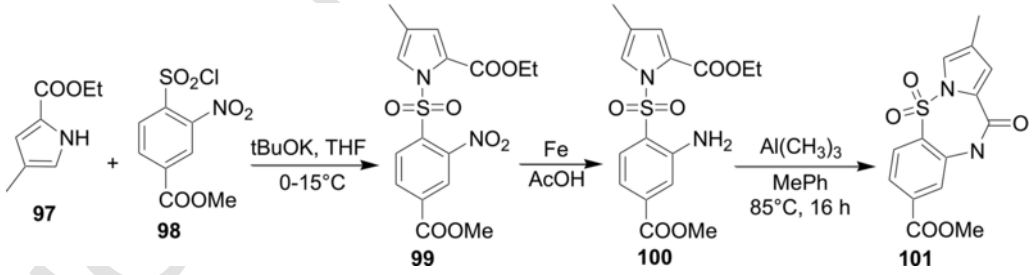
7-Bromo-3-butyl-3-ethyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine-1,1-dioxide **96** was synthesized from corresponding 2-ethyl-N1-phenylhexane-1,2-diamine **93** and 2,4-Dibromo-5-methoxybenzenesulfonyl chloride **94.**[30] The reaction of 6-1 and 6-2 in THF at 0 °C in the presence of triethylamine after 16 h leads to the formation of the desired 2,4-dibromo-5-methoxy-*N*-(3-((phenylamino)methyl)heptan-3-yl)benzenesulfonamide **95** (see **Scheme 32**). After chromatographic purification authors managed to obtained **95** in 59% yield. Further cyclization of sulfonamide **95** was performed in DMF solution under the action of potassium carbonate and copper powder at 150 °C for 24 h. Chromatogracally purified target 1,2,5-thiadiazepine **96** was obtained in 83% yield.

Wang et al. have described the synthesis of tricycle compound with condensed 1,2,5-thiadiazepine moiety.[31] The multi-step synthesis is presented in **Scheme 33**. Pyrrole **97** was mixed with potassium *tert*-butoxide, and then the solution of sulfochloride **98** was added dropwise with continuous stirring maintaining the temperature about 0–10 °C. The reaction time was about 16 h. Product **99** was obtained as a pale yellow solid. Reduction of the nitro group by iron powder in glacial acetic acid leads to the amino derivative **100**, which was separated as white solid. Next cyclization of **100** to condensed pyrrolo[1,2-b][1,2,5]benzothiadiazepine **101** have been performed via the action of trimethyl aluminum in toluene under the heating at 80–85 °C for 16 h.

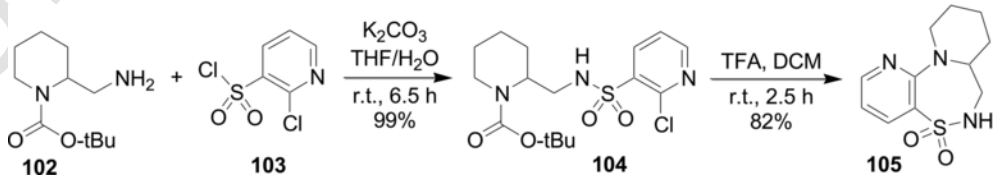
Barbey and co-authors have patented a study on Inhibitors of KEAP1-Nrf2 protein-protein interaction.[32] As a precursor for numerous synthesized compound they have explored 7,7a,8,9,10,11-hexahydro[2,1-d:2′,3′-f][1,2,5]thiadiazepine 5,5-dioxide **105**. The reaction of *tert*-butyl 2-(aminomethyl)piperidine-1-carboxylate **102** with 2-chloropyridine-3-sulfonyl chloride **103** in the presence of potassium carbonate in THF-water mixture leads to the formation of sulfamide **104** in excellent yield (99%). The reaction was performed at room temperature for 6,5 h (see **Scheme 34**). Further cyclization of **104** was done by the action of trifluoroacetic acid in dichloromethane at room temperature during 2.5. After flash chromatography purification the yield to the tricyclic 7,7a,8,9,10,11-hexahydro[2,1-d:2′,3′-f][1,2,5]thiadiazepine 5,5-dioxide **105** equals 82%.



Scheme 32



Scheme 33



Scheme 34

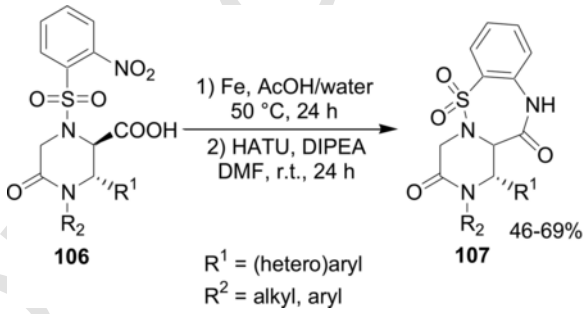
Preparative synthesis of a novel version of the medicinally relevant 1,2,5-benzothiadiazepin-4-one-1,1-dioxides **107** have been developed by Usmanova et al.[33] The proposed pathway utilizes modified piperazin-2-ones **106** as starting precursors, which can be obtained by the Castagnoli-Cushman reaction.[33] Optimized synthesis includes the iron reduction of the nitro group in *o*-nitrobenzenesulfonyl fragment in aqueous acetic acid at 50 °C for24 h (see **Scheme 35**). Further lactamization under promotion by 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) gave a satisfactory yield (46–69%) of the target cyclization products **107**. According to the single-crystal X-ray analysis, the relative stereochemistry remained trans.

Heightman et al., continuing their work on the discovery of highly potent compounds that can be used to probe the biology associated with directly disrupting the interaction of NRF2 with the KEAP1 Kelch domain, have presented an optimization of protein − ligand interactions in three energetic "hot spots" identified by fragment screening.[34] Authors have explored compound **111**, which contains 1,2,5-thiadiazepine moiety. The synthesis starts from 2-fluorosulfonamide **108**, which after microwave-heated reaction with 2-(methylamino)ethanol and under the action of diisopropyl azodicarboxylate (DIAD) and polymer-supported triphenylphosphine (PS-PPh_3) was transformed into benzothiadiazepine **109** (**Scheme 36**). Further involving of **109** into Mitsunobu coupling with ethyl 3-(3-(hydroxymethyl)phenyl)-3-(7-methoxy-1-methyl-1Hbenzo[d][1,2,3]triazol-5-yl)propanoate **110** under the action of DIAD and PS-PPh_3 in tetrahydrofuran leads to the intermediate ester which was hydrolyzed to the target acid **111** with 34% yield.

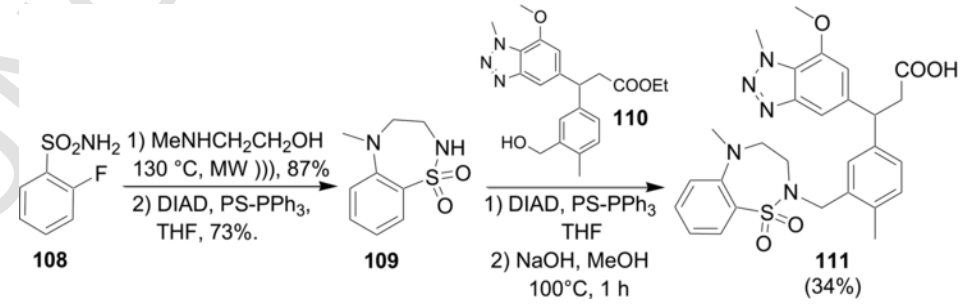
Polymer-supported stereoselective synthesis of benzoxazino[4,3-b][1,2,5]thiadiazepinone 6,6-dioxides **114** described in the work of Kralova et al.[35] Final stages of synthesis include: (a) the releasing of a molecule from a polymer (Wang resin) and cleavage of a protecting group with a simultaneous formation of a X-N six-membered cycle; (b) formation of 1,2,5-thiadiazepinone cycle. At first, polymer-supported derivatized amino acids **112** were treated with trifluoroacetic acid in dichloromethane at room temperature to form oxa/thia-zines **113**. Further reflux of **113** in toluene or dichloroethane (ethylene dichloride—EDC) in the presence of toluenesulfonic acid leads to the desired target compounds **114** (**Scheme 37**).

During the investigation of N-alkylation and aminohydroxylation of 2-azidobenzenesulfonamides, Hamasharif and co-workers have found a route to pyrrolobenzothiadiazepine.[36] Cyclization of pentenyl fragment of **115** leads to (1-[(2-azidophenyl)sulfonyl]pyrrolidin-2-yl)methanol **116** (**Scheme 38**). Oxidation of hydroxyl group with oxalyl chloride in the presence of DMSO produces (1-[2-azidobenzenesulfonyl]pyrrolidin-2-yl)-carbaldehyde **117**. In theory, treatment of **117** with the Bestmann-Ohira reagent in methanol will produce the corresponding alkyne; however, the authors have isolated the product of ethynyl and azido groups coupling pyrrolo[1,2-b][1,2,3]triazolo[5,1-d][1,2,5]benzothiadiazepine 8,8-dioxide **118** in 70% yield.

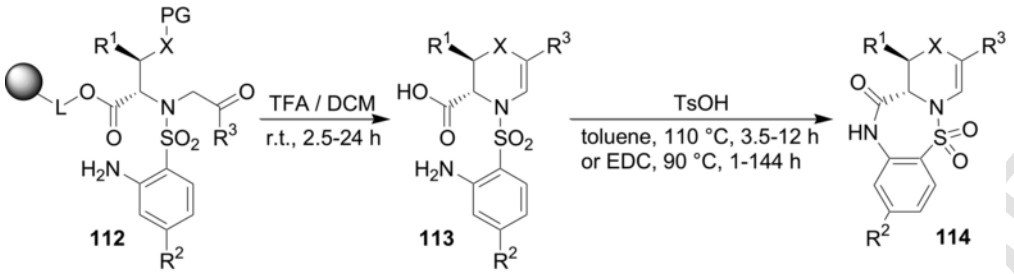
Solid-phase synthesis of 2,3-dihydrobenzo[f][1,2,5]thiadiazepin-4(5H)-one 1,1-dioxides **120** was developed by Trapani and co-authors.[37] The final stage of the proposed multi-step synthesis is the cleavage of the sulfamide moiety from resin **119** via treatment with 50% trifluoroacetic acid in dichloromethane and next cyclization with thionyl chloride (**Scheme 39**).



Scheme 35



Scheme 36



X = O, S

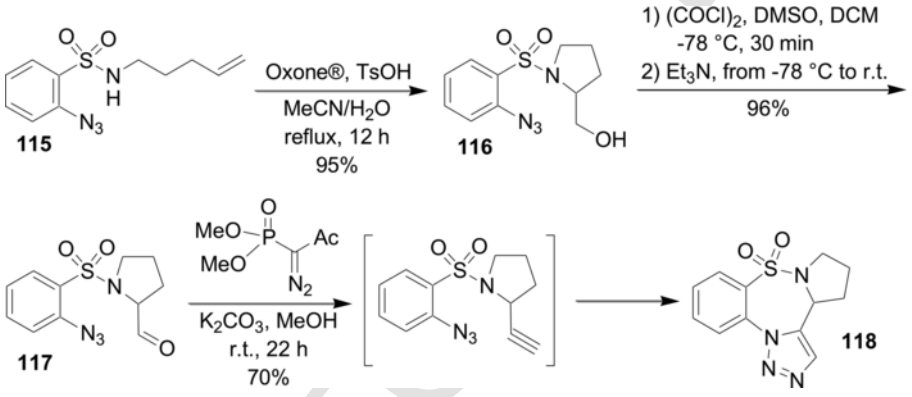
X-PG = O-*t*Bu, S-Trt

R^1 = H, Me

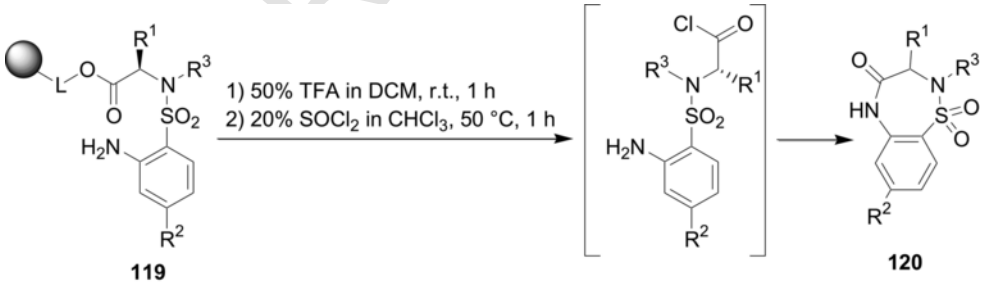
R^2 = H, MeO, Cl, CF_3, NH_2

R^3 = 4-Br-Ph, Ph, 4-Me-Ph, 4-CF_3-Ph, 3-thiazolyl, 4-NH_2-3,5-$(Cl)_2$-Ph

Scheme 37



Scheme 38



R^1 = Me, Bn, CH_2CH_2COOMe, $CH_2CH_2CONHPr$, CH_2CH_2CO-N-morfoline, (4-imidazolyl)methyl

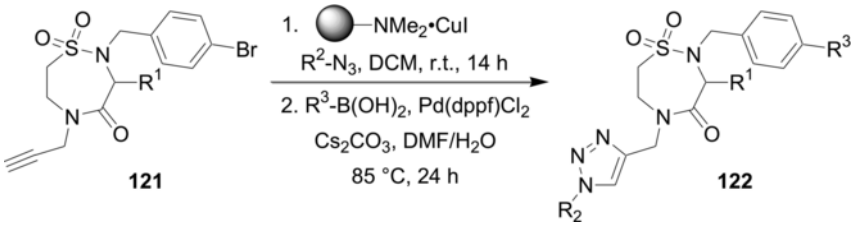
R^2 = H, MeO, Cl, CF_3

R^3 = Me, Et, Bn, 3-(4-pyridyl)propyl, $CH_2CH_2NEt_2$, CH_2CH_2OMe

R^2+R^3 = $(CH_2)_3$

Scheme 39

The automated parallel synthesis was used to prepare 184 sultams **122.**[38] The authors have prepared three sultam core scaffolds **121** based upon an aza-Michael reaction on a multifunctional vinyl sulonamide (**Scheme 40**). Sequential two-step Huisgen cycloaddition and Pd-catalyzed Suzuki-Miyaura coupling sequence were used for generating the sultams library.



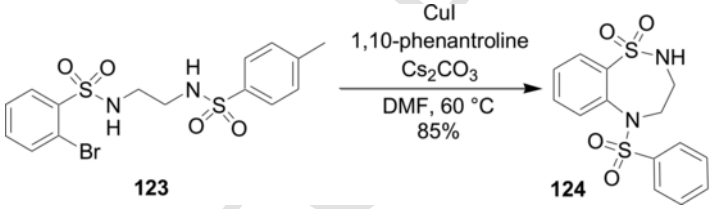
Scheme 40

Rolfe et al. have reported a strategy to probe chemical and biological space via a "Click, Click, Cyclize" protocol.[39] The authors have synthesized sulfonamides under cyclization protocols (**Scheme 41**). Cu-catalyzed N-arylation cyclization was used for the synthesis of the sultam **124** from disulfamide **123** in 85% yield.

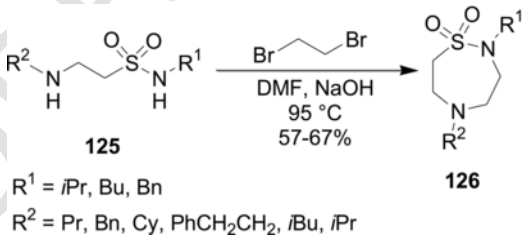
Niu et al. have synthesized a series of seven- and eight-membered ring sultams.[40] The interaction of disubstituted β-amino sulfamides **125** with 1,2-dibromoethane leads to 1,2,5-thiadiazepane 1,1-dioxides **126** in good yield (**Scheme 42**).

Tetrazolo- and 1,2,4-oxadiazolo-fused derivatives of pyrrolo[2,1-c][1,4]benzodiazepines and pyrrolobenzothiadiazepines have been produced and investigated by Hemming et al.[41] The tetrazolo-fused systems **128** were produced by intramolecular 1,3-dipolar cycloaddition between an azide **127** and a nitrile (**Scheme 43**).

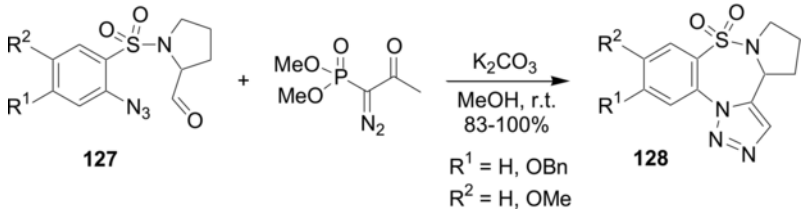
Majumdar and co-workers have developed an efficient one-pot strategy for the synthesis of triazolobenzothiadiazepine 1,1-dioxides **130** by the reaction of 2-azido-N-substituted benzenesulfonamides **129** with propargyl bromides.[42] The reaction was carried out in basic alumina under microwave irradiation for 10 min (**Scheme 44**).



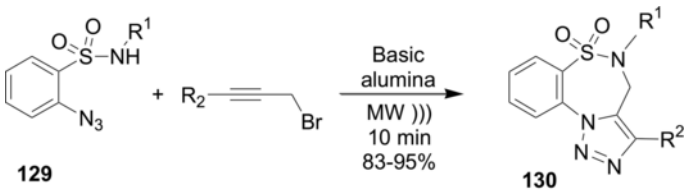
Scheme 41



Scheme 42



Scheme 43



R^1 = Ph, 4-Cl-Ph, 4-Me-Ph, 4-MeO-Ph, Bn, propynyl
1-naphthyl, 2*H*-chromen-2-on-6-yl
R^2 = H, Me

Scheme 44

The thiadiazepines **132** have been obtained via thermolysis of 2-azido benzosulfamides **131** above 208 °C in diphenyl ether.[43] Direct N-C-type amination of the amino-group activated ring provided the target compounds **132** in 67–85% yield, except the compound with R equals COOEt, which was isolated in 12% yield (**Scheme 45**).

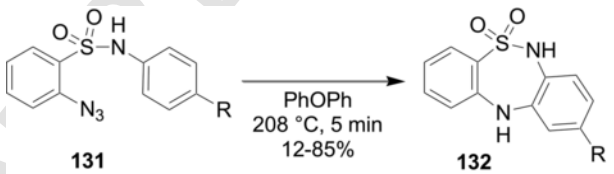
Asad et al. have developed a one-pot sequential protocol for obtaining sultams **133** in a highly scalable manner.[44] The synthesis includes three steps: (1) sulfonation of primary amines with 2-chloroethylsulfonyl chloride; (2) Michael addition of 2-aminoacids; (3) intramolecular amide coupling (**Scheme 46**).

8 1,4,5-Thiadiazepane

Nguyen and Peet have presented a new route to esters of (E)-2-(styrylsulfonyl)acetic acid.[45] The reaction of the ethyl ester **134** with hydrazine hydrate in ethanol at 65 °C gave a separable 1.2:1 mixture of the seven-membered 6-phenyl-1,4,5-thiadiazepane-3-one 1,1-dioxide **135** and the six-membered 4-amino-5-phenylthiomorpholine-3-one 1,1-dioxide **136** (**Scheme 47**).

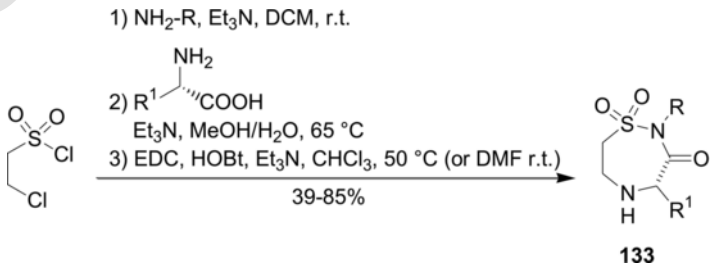
The interaction of azoalkenes derived **137** with pyridinium 1,4-zwitterionic thiolates **138** undergoes via [4 + 3] cascade cyclization mechanism.[46] The reaction was performed in dichloromethane in the presence of sodium carbonate (**Scheme 48**). A library of highly functionalized 2,5-dihydro-1,4,5-thiadiazepines **139** was obtained in moderate and high yield.

Further oxidation of 2,5-dihydro-1,4,5-thiadiazepines **139** under the 1 equiv. and 3 equiv. of *m*-chloroperbenzoic acid in dichloromethane at room temperature leads to sulfoxide **140** and sulfone **141** analogs, respectively[46] (**Scheme 49**).

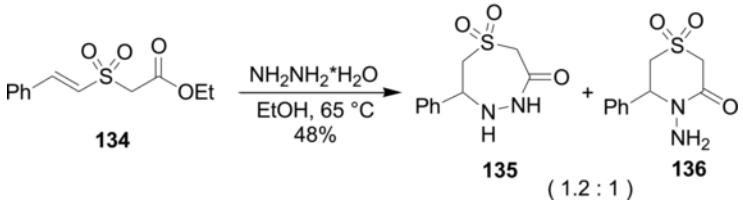


R = H, F, Cl, Br, OMe, COOEt

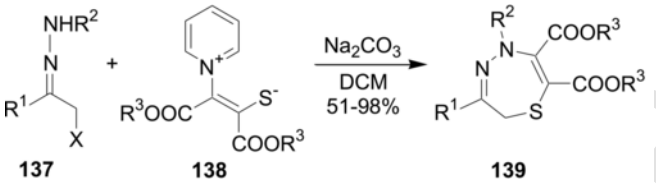
Scheme 45



Scheme 46

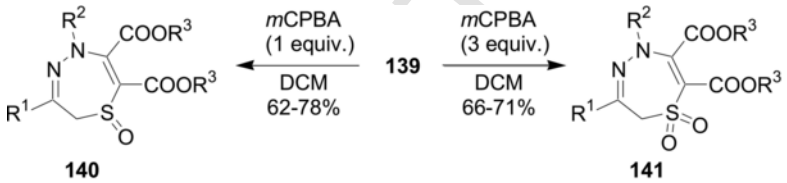


Scheme 47



R^1 = Ph, 4-MeO-Ph, 4-Me-Ph, 4-NO_2-Ph, 4-CF_3-Ph, 4-F-Ph, 2-Furyl, *t*Bu, *(E)*-Styrenyl
R^2 = Ac, Boc
R^3 = Me, Et
X = Br, Cl

Scheme 48



R^1 = Ph, 4-MeO-Ph, 4-Me-Ph, 4-NO_2-Ph, 4-CF_3-Ph, 4-F-Ph, 2-Furyl, *t*Bu, *(E)*-Styrenyl
R^2 = Ac, Boc
R^3 = Me, Et

Scheme 49

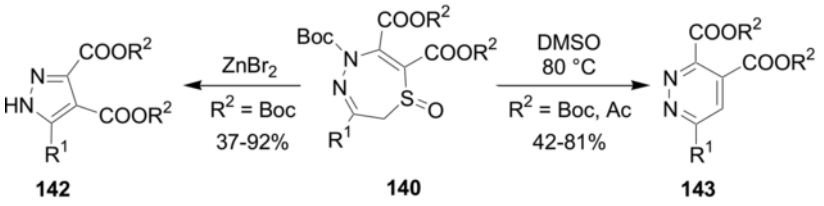
Cheng et al. have explored switchable ring-contractive extrusion reactions of sulfoxides.[47] Dihydro-1,4,5-thiadiazepine S-oxides **140** were used as starting precursors for obtaining pyridazines **143** under thermal conditions or pyrazoles **142** under Lewis acid-mediated conditions (**Scheme 50**).

González-Muñoz, with co-authors have explored neuroprotective properties of dibenzo[1,4,5]thiadiazepines **146** and their potential usefulness in the treatment of neurodegenerative diseases.[48] Acylation of hydrazine-substituted diphenyl sulfides **144** under the action of acetyl chloride in toluene leads to corresponding diacetyl derivatives **145** (**Scheme 51**). Further cyclization of hydrazides **145** was taken with potassium carbonate in dimethylformamide and refluxed for 15 min.

Rahimizadeh and co-authors have studied the reaction of substituted 2-thiocyanoacetophenones and hydrazine hydrate as a pathway for the preparation of 1,4,5-thiodiazepines.[49] 2-Thiocyano acetophenones **147** in ethanol were treated with hydrazine hydrate and concentrated HCl, and the resulting mixture was heated under reflux for 18 h resulting in the target thiadiazepines **148** (**Scheme 52**).

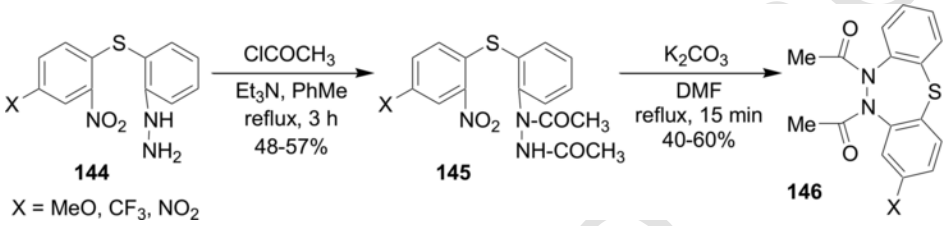
9 1,5,2-Dioxazepane

Petrov and Marshall have converted cyclic perfluorinated imidoyl fluoride **149** into the corresponding oxaziridine **150** under mild conditions.[50] *meta*-Chloroperoxybenzoic acid was placed in dry acetonitrile, and the resulting solution was precooled to about 5 °C

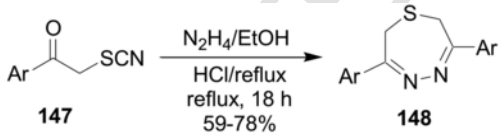


R^1 = Ph, 4-MeO-Ph, 4-Me-Ph, 4-NO_2-Ph, 4-CF_3-Ph, 4-F-Ph, 2-Furyl, *t*Bu, *(E)*-Styrenyl
R^2 = Me, Et

Scheme 50



Scheme 51



Ar = Ph, 4-Me-Ph, 4-Cl-Ph, 4-Br-Ph, 4-MeO-Ph, 3-NO_2-Ph

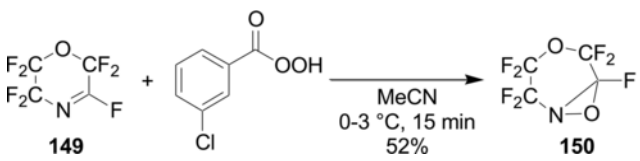
Scheme 52

(**Scheme 53**). Imidoyl fluoride **149** was added dropwise, and the reaction mixture was allowed to stand 15 min at 0–3 °C. The yield of the final compound **150** with the perfluoro-1,5,2-dioxazepane moiety equals 52%.

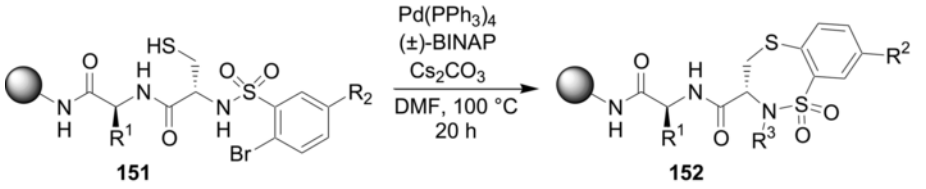
10 1,5,2-Dithiazepane

Chen et al. have developed the solid-phase synthesis of skeletally diverse benzofused sultams.[51] One of the key step of the proposed synthetic route is the palladium-catalyzed cyclization under nitrogen (**Scheme 54**). The resin **151**, cesium carbonate, $Pd(PPh_3)_4$ and (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((±)-BINAP) were mixed with anhydrous DMF, and the resulting mixture was heated at 100 °C for 20 h producing **152** that contains 1,5,2-dithiazepane core.

A novel and Cu(I)-catalyzed one-pot regio- and stereospecific synthesis of benzo[1,5,2]dithiazepine 1,1-dioxides **154** by cyclization of functionalized propynamides **153** with elemental sulfur has been developed[52] (**Scheme 55**).

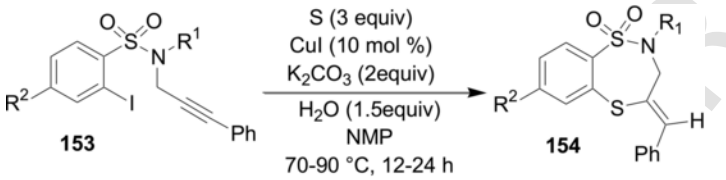


Scheme 53



R^1 = H, Me, *i*Pr, *i*Bu, $MeSO(CH_2)_2$, $HOCH_2$
R^2 = H, CF_3
R^3 = H, Et, 4-NO_2PhCH_2, 2,4-F_2PhCH_2, $PhCOCH_2$

Scheme 54



R^1 = Me, Ph
R^2 = Me, *t*-Bu,

Scheme 55

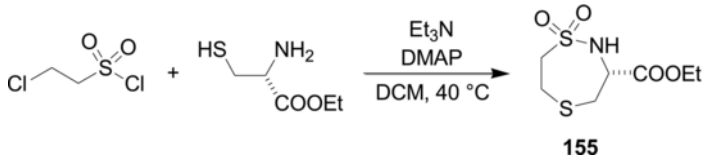
Zang et al. have synthesized a library of 1,5,2-dithiazepine 1,1-dioxides.[53] A prime precursor 3-carbethoxy-1,5,2-dithiazepine 1,1-dioxide **155** was obtained via the reaction of 2-chloroethanesulfonyl chloride with cysteine in the presence of triethylamine and *p*-dimethylaminopyridine (**Scheme 56**).

11 1,2,5-Dithiazepane

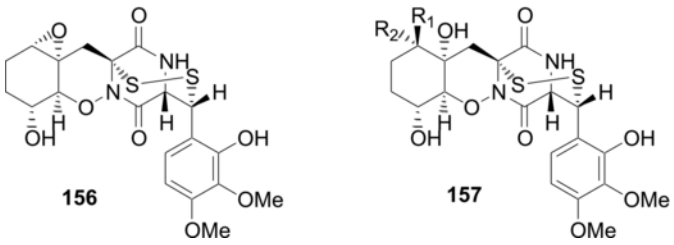
Yamazaki et al. have isolated new antibiotics from the marine-derived fungus Trichoderma sp. TPU199 (cf. Trichoderma brevicompactum).[54] Two of these, namely pretrichodermamide A **156** and gliovirin **157**, possess a rare type of epipolythiodiketopiperazine (ETP) structure and contain 1,2,5-dithiazepane ring with a disulfide bridge between the α- and β-positions of two amino acid fragments (**Scheme 57**). The authors have used NMR (^1H, ^{13}C, ^1H-^1H COSY, and HMBC), UV, CD, and IR spectra for the correct determination of the structure of the newly extracted compounds.

Harwoko et al. have isolated two dithiodiketopiperazines **158** and **159** produced by the endophytic fungi *Trichoderma harzianum* (**Scheme 58**). 1D/2D NMR and HRESIMS techniques were used for the establishment of the new compound **158**. Moreover, the authors have investigated their antifungal, antibacterial, and cytotoxic potential of the isolated compounds against various microorganisms and cell lines. High antimicrobial activity towards *Ustilago maydis* and *Mycobacterium tuberculosis* was determined for the Pretrichodermamide A **159.**[55]

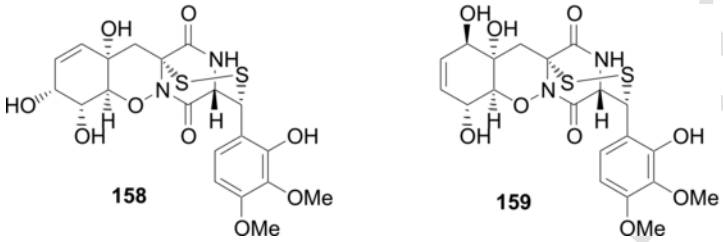
In the report on the syntheses of a range of "bimanes" decorated with various glycosyl residues, the authors have described the synthesis of bimane fused with dithiazepane ring.[56] To a solution of 4,6-bis-[bromomethyl]-3,7-dimethyl-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione **160** in dichloromethane potassium thioacetate was added (see **Scheme 59**). Stirring of the suspension at room temperature for 1.5 h and next separation of the product produces yellow needles of 4,6-bis-[(acetylthio)methyl]-3,7-dimethyl-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione **161** in 62% yield. Further treatment of methanol solution of **161** with acetylchloride at room temperature overnight produces 4,6-bis-(mercaptomethyl)-3,7-dimethyl-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione **162** which was



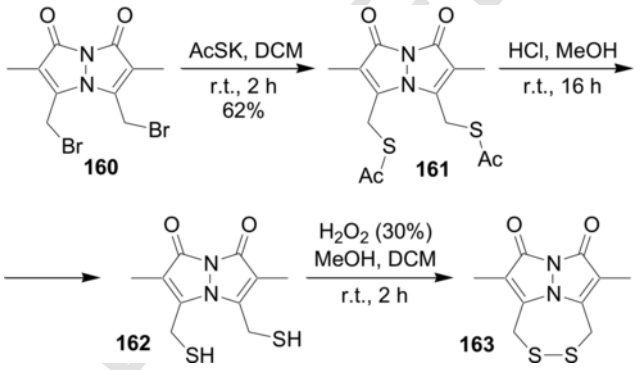
Scheme 56



Scheme 57



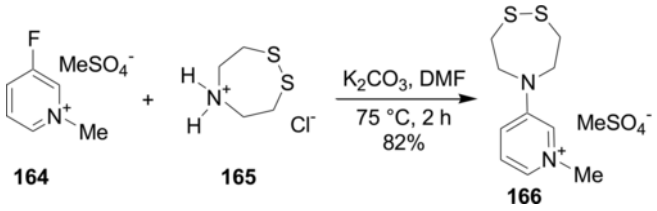
Scheme 58



Scheme 59

separated as yellow needles in 87% yield. Oxidation of **162** was performed in methanol-dichloromethane mixture via addition of 30% hydrogen peroxide. The target product 4,6-(dithiamethylene)-3,7-dimethyl-1,5-diazabicyclo[3.3.0]octa-3,6-diene-2,8-dione **163** was separated in 63% yield as a yellow solid.

Arylation of 1,2,5-dithiazepane hydrochloride **165** can be performed by the action of 3-fluoro-1-methylpyridin-1-ium methylsulfate **164** in DMF in the presence of potassium carbonate (**Scheme 60**). The reaction mixture was magnetically stirred at 75 °C for 2 h. The target 3-(1,2,5-dithiazepan-5-yl)-1-methylpyridin-1-ium methylsulfate **166** was obtained as a pale yellowish solid in 82% yield. The synthesis was patented by Zhang et al.[57]



Scheme 60

Tsunematsu, with co-authors, have explored biosynthetic retro-aldol amino acid conversion to form the antifungal agent aspirochlorine.[58] Numerous structures contain 1,2,5-dithiazepane moiety **167–169** were detected by authors (**Scheme 61**).

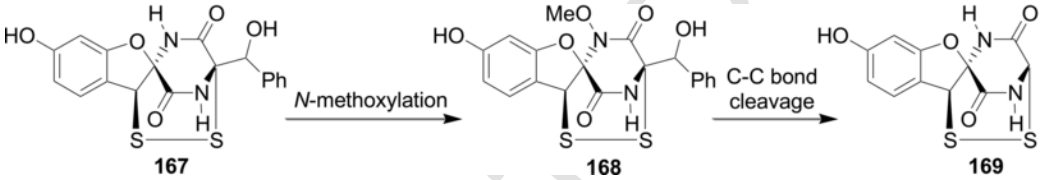
Melnyk and Agouridas have summarized literature data on using perhydro-1,2,5-dithiazepine **170** (**Scheme 62**) in the synthesis of thioesters, thioacids, amides, peptides, and in preparation of metal-containing complexes.[59]

12 1,4,5-Oxadithiepane

Kim et al. have designed 1,4,5-oxadithiepan-2-one **172**, which can be considered as ε-caprolactone, where two CH_2 fragments are replaced with -S-S-group.[60] The precursor **171** was obtained through the esterification reaction of 2-mercaptoethanol and 2-thioglycolic acid in the presence of *p*-toluenesulfonic acid as catalyst (**Scheme 63**). The reaction mixture was stirred at 50 °C for 3 days. 2-Mercaptoethyl 2-mercapto acetate **171** was obtained as a pale yellow oil in 65% yield. Further catalytic oxidative cyclization of **171** by the mixture of sodium iodide and hydrogen peroxide in ethyl acetate leads to the formation of target 1,4,5-oxadithiepan-2-one **172** as a pale yellow oil in 60% yield.

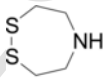
Authors have figured that 7-membered **172** may provide sufficient ring strain for synthesis of polymer **173** (**Scheme 64**). Synthetic screening of various acid-base catalysts shows that in most cases, the disulfide bonds were labile to the action of the catalyst. Fortunately, diphenylphosphoric acid showed simultaneously high tolerance to the disulfide bond and great catalytic activity in 1,4,5-oxadithiepan-2-one **172** polymerization reaction.

Czub et al. have investigated acute aquatic toxicity of sulfur mustard and its degradation products to *Daphnia magna*.[61] Derivative **174**, when reacts with sodium disulfide, produces 1,4,5-oxadithiepane **175** (**Scheme 65**).



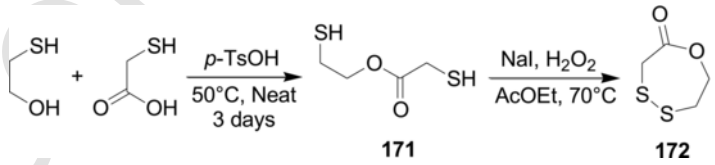
167 **168** **169**

Scheme 61



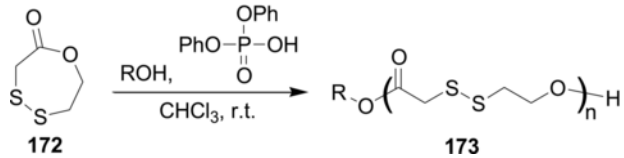
170

Scheme 62



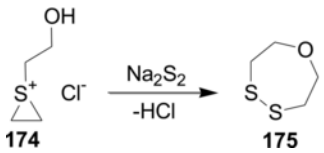
171 **172**

Scheme 63



172 **173**

Scheme 64



Scheme 65

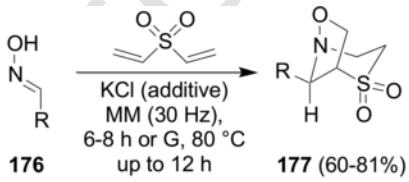
13 1,5,2-Oxathiazepane

Paper by Bhutia et al. describes tandem Michael addition-1,3-dipolar cycloaddition of aldoximes **176.**[62] The authors have developed a powerful method for obtaining 7-oxa-4-thia-1-aza-bicyclo[3.2.1]-octane 4,4-dioxides **177**. The reaction was taken in stainless steel milling vessel. Corresponding aldehyde, hydroxylamine chloride, and potassium carbonate were charged in the vessel for the formation of the aldoximes (**Scheme 66**). Divinyl sulfone and KCl were added, and the resulting mixture was milled further. Final products were extracted and purified by column chromatography.

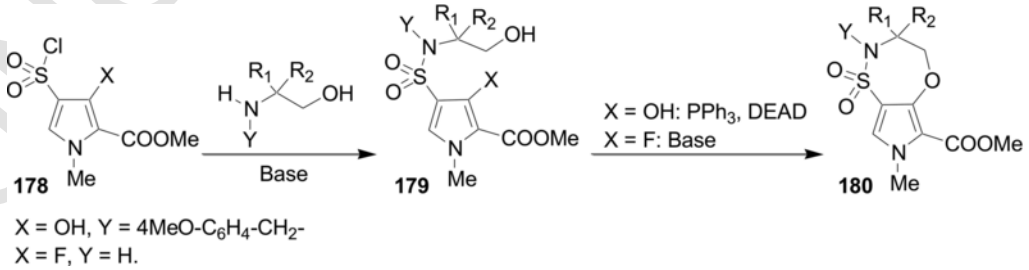
14 1,4,5-Oxathiazepane

Beigelman and Smith have patented the synthesis of compounds **180**, which contain 1,4,5-oxathiazepane heterocycle.[63] Authors proposed the reaction of pyrrole sulfonyl chlorides **178** with appropriate "protected" or free 2-aminoethanols in the presence of a base (inert amine) with the formation of corresponding sulphonamides (see **Scheme 67**). In the case of OH-substituted pyrroles and PMB protected sulphonamide group, utilizing Mitsunobu reaction conditions, the sulphonamides **179** cyclized with the formation of an oxygen-containing 7-membered ring. Similarly, in the case of fluoro-substituted pyrrole sulphonamides 5-5, under basic conditions, the analogs 7-membered ring **180** can be formed. It must be noticed that fluoro-pyrroles gives the possibility to obtain 1,4,5-oxathiazepanes 5-6 from unprotected 2-aminoethanols.

Abnormal structural parameters related to sulfonamide bond in a raw of sultams have been studied in detail in the work of Blahun et al.[64] A series of tertiary aliphatic sulfonamides have been studied via crystallographic and quantum chemical methods. It was established



Scheme 66



Scheme 67

that the properties of the S–N bond are most-dependent upon the character of the nitrogen lone pair. The authors explored Paquette's sultams—bicyclic sultams with a bridgehead nitrogen atom. One of the studied structures was 4-oxa-7-thia-1-azabicyclo[3.2.1]octane-7,7-dioxide **182**, which was synthesized upon stirring of starting sulfonyl fluoride salt **181** in dry acetonitrile in the presence of potassium carbonate (**Scheme 68**). The target sultam **182** was obtained as colorless crystals in 66% yield.

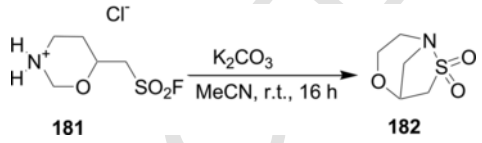
De Francesco et al. have patented new tricyclic inhibitors of the hepatitis b virus.[65] They have used pyrrole-2-carboxamides **183** for the synthesis of pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxides **184** (see **Scheme 69**). The reaction was performed under the action of cesium carbonate in DMF. The reaction mixture was heated at 130 °C for 45–60 min under microwave irradiation.

Intramolecular cyclization of epoxide-tethered 2-fluorobenzenesulfonamides **185** leads to 1,4-benzoxazine-fused benzoxazepine-1,1-dioxides **186** in good yields (72–90%).[66] Conditions optimized synthesis based on the use of sodium hydride in DMF at room temperature for 4 h (see **Scheme 70**).

Heightman et al. have explored highly potent compounds that directly disrupt the interaction of NRF2 with the KEAP1 Kelch domain.[34] The authors have designed a series of 1,4,5-oxathiazepines **189**. The synthesis starts from 2-fluorosulfonyl chloride **187**, which after microwave-heated reaction with substituted 2-aminoethanols and under the action of diisopropyl azodicarboxylate (DIAD) and polymer-supported triphenylphosphine (PS-PPh_3) were transformed into benzothiazepine **188** (**Scheme 71**). Further Mitsunobu coupling of **188** with ethyl 3-(3-(hydroxymethyl)phenyl)-3-(7-methoxy-1-methyl-1Hbenzo[d][1,2,3]triazol-5-yl)propanoate **110** under the action of DIAD and PS-PPh_3 in tetrahydrofuran leads to the intermediate ester which was hydrolyzed to the target acid **189** with 56–90% yields.

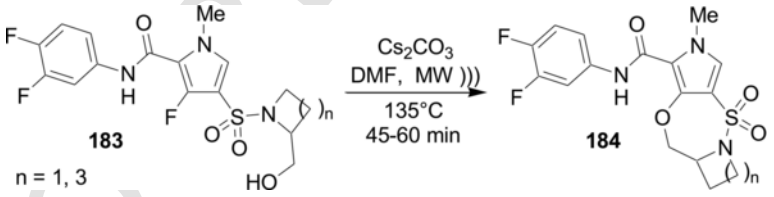
Borgohain and co-authors have developed a multistep synthesis of tetrahydroquinoline-embedded bridged benzothiazepine-1,1-dioxides **192.**[67] N-alkylation of *N*-aryl-2-fluorobenzenesulfonamides **190** with trans-2,3-epoxy cinnamyl alcohols tosylates **191** was taken in DMF at 60 °C for 12 h. Potassium carbonate was added to make basic conditions. Next transformation of trans-2,3-epoxy cinnamyl N-alkylated products under the action of toluenesulfonic acid hydrate in toluene at 80 °C leads to *N*-sulfonyl tetrahydroquinolines. Finally, treatment with sodium hydride in DMF at room temperature leads to a quick formation of target compounds **192** with benzo-1,4,5-oxathiazepane moiety (see **Scheme 72**).

A novel strategy to construct dibenzo[b,f][1,4,5]oxathiazepine 5,5-dioxides was proposed in the work of Sapegin et al.[68] Authors have found that secondary *o*-hydroxybenzene sulfonamides **194** can be explored as bis-electrophilic reagents with (het)aryl structures **193** with



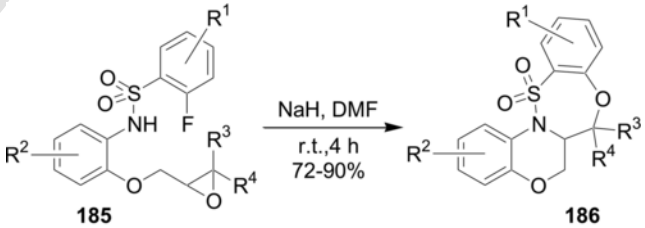
181 **182**

Scheme 68



183 **184**

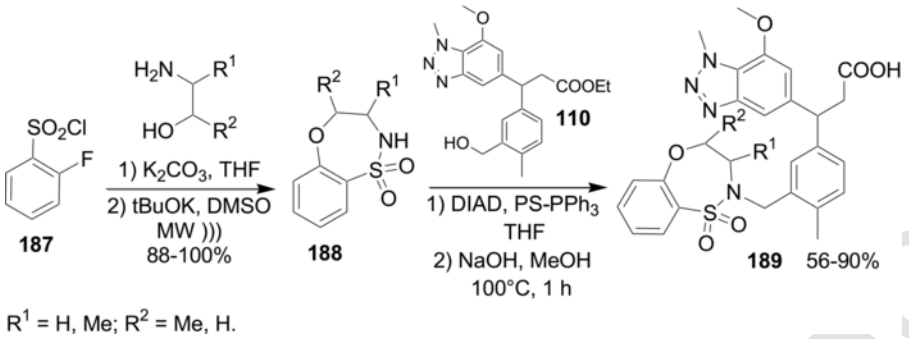
Scheme 69



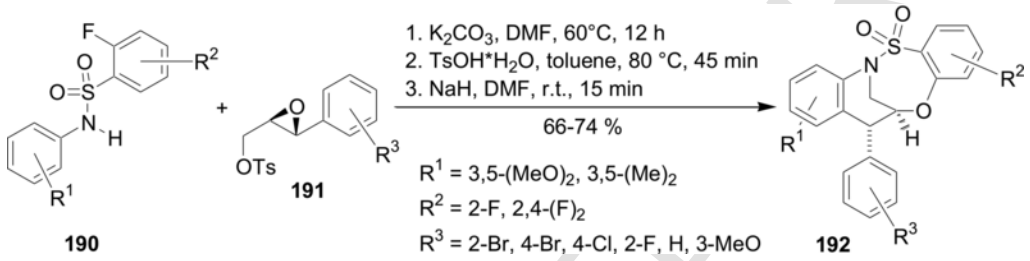
185 **186**

R^1 = H, 3-F, 4-F, 5-F, 5-Br
R^2 = H, 5-Me, 4-OMe, 4-Br
R^3 = H, Me, *n*-Pr
R^4 = H, Me

Scheme 70



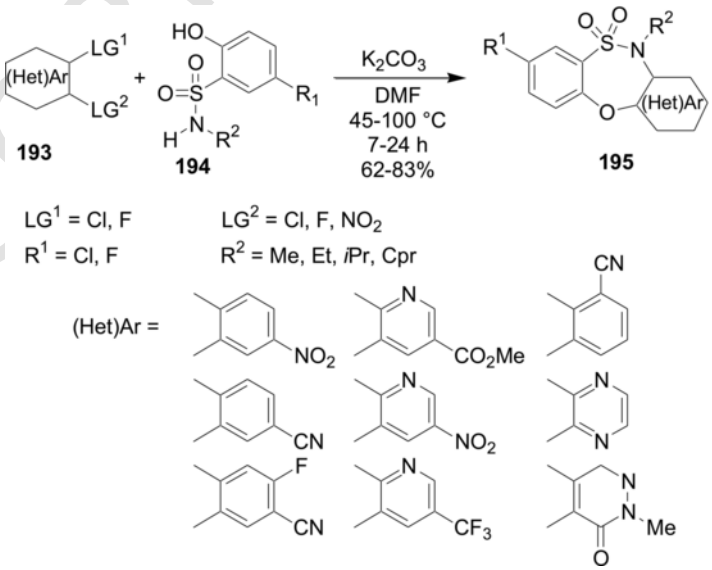
Scheme 71



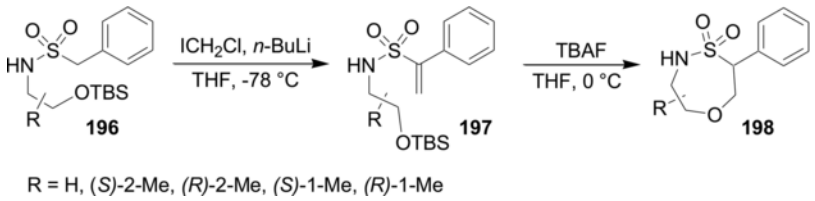
Scheme 72

two good *o*-leaving groups to produce tricyclic dibenzo[b,f][1,4,5]oxathiazepine-5,5-dioxides and their heterocyclic analogs **195** (**Scheme 73**). The reaction proceeds in DMF under medium heating during 7–24 h. The target compounds were obtained regiospecifically in good to excellent yields.

Modification of the δ-sultam ring led to the discovery of more polar oxasultam.[68] Introduction of methylidene group into *tert*-butyldimethylsilyl-protected substrates **196** via the action of chloroiodomethane in THF in the presence of butyllithium at − 78 °C leads to precursors **197** (**Scheme 74**). Next treatment with tetrabutylammonium fluoride causes the formation of **198** with 1,4,5-oxathiazepane core.



Scheme 73



Scheme 74

Haftchenary et al. have synthesized 7-membered sultams starting from substituted 2-aminoethanols **199.**[69] At first, the transformation of the alcohol group into *tert*-butyldimethylsilyl (TBS) ether was performed (**Scheme 75**). Next treatment with 2-chloroethanesulfonyl chloride in the presence of triethylamine produces the vinyl sulfonamide intermediates. Further *N*-methylation afford N-Me-sulfonamides in 70–90% yields. Lastly, tetrabutylammonium fluoride (TBAF) promotes intramolecular cyclization via *tert*-butyldimethylsilyl group cleavage and formation of target 1,4,5-oxathiazepane-5,5-dioxides **200** in low to high yields (37–97%).

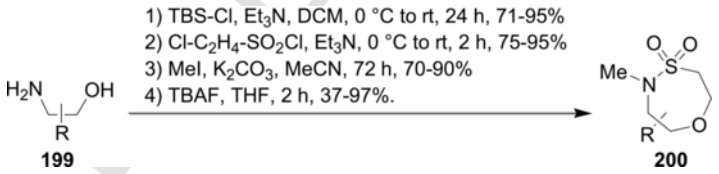
Faisal et al. have explored the application of silica-supported alkylating reagents in the synthesis of benzoxathiazepine 1,1-dioxides.[70] The proposed synthetic route starts from the reaction of 2,4-difluorobenzenesulfonyl chloride **201** with a chiral 2-aminopropanol in dimethylformamide at room temperature in the presence of triethylamine. Next cyclization of sulfonamide **202** to benzoxathiazepine 1,1-dioxide **203** was performed via cesium carbonate treatment in dimethylformamide under microwave conditions at 140 °C (**Scheme 76**).

Huang et al. have applied diversity-oriented synthesis as a route to three-dimensional fragments, which can be useful in drug discovery.[71] Authors proposed a synthesis of **205** starting from reduction of proline, next protection with *tert*-butyldimethylsilyl (TBS) chloride, and further coupling 2-chloroethanesulfonyl chloride to give **204**. The final removal of the TBS-group causes intramolecular cyclization with the formation of the target **205** (see **Scheme 77**).

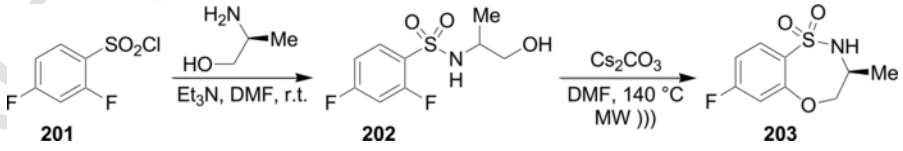
Rolfe and colleagues have developed a facile synthesis of a library of benzothiaoxazepine-1,1′-dioxides.[72] 2,6-Difluorobenzene sulphonamide **206**, cesium carbonate, benzyltriethylammonium chloride, and epoxide were mixed in dimethylformamide (**Scheme 78**). The resulting mixture was heated under microwave irradiation. Target benzothiazepine-1,1′-dioxides **207** were isolated in good yields.

The oxa-Michael cyclization reaction between epoxides and various vinylsulfonamides **208** in 1,4-dioxane or tetrahydrofuran leads to sultams **209** in good yield and high crude purity[73] (**Scheme 79**).

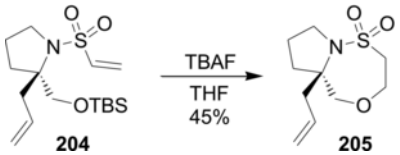
ROMP-derived oligomeric phosphate can be applied in facile benzylation.[74] To show the versatility of ROMP-based oligomeric benzyl phosphates (OBP) Long et al. have explored a benzylation reaction of benzothiazepine-1,1-dioxides **210** (**Scheme 80**). The OBP and model sultam **210** were mixed in tetrahydrofuran, and the resulting mixture was treated with potassium carbonate and



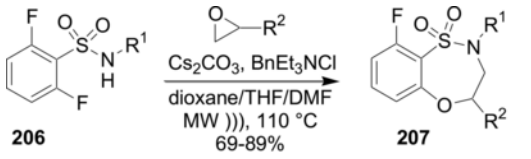
Scheme 75



Scheme 76



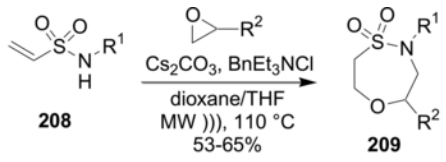
Scheme 77



206 207

R^1 = Bu, propargyl, PhCH(Me), Cpr, 4-MeO-Bn, Cyp
R^2 = $BnOCH_2$, $PrOCH_2$, $PhOCH_2$, 3-butenyl, $PrC(O)OCH_2$

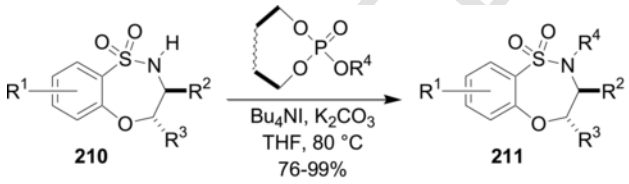
Scheme 78



208 209

R^1 = allyl, Bu, Bn, propargyl, PhCH(Me), Cyp
R^2 = $BnOCH_2$, 4-Me-$PhOCH_2$, $PrOCOCH_2$, $PhOCH_2$

Scheme 79



210 211

R^1 = 4-Br, 3-Cl, 5-Cl
R^2 = Ph, *i*Bu, Me
R^3 = H, Ph
R^4 = Bn, 3,5-$(MeO)_2$-Bn, 4-F-Bn, 2-Me-Bn, 4-Cl-Bn

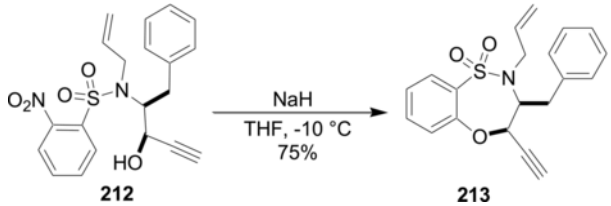
Scheme 80

tetrabutylammonium iodide under stirring at 80 °C overnight. Target benzyl-substituted sultams **211** were obtained in good and excellent yield.

Pizzirani et al. have explored different intramolecular cyclizations of diastereoisomeric amino propargylic alcohols.[75] Treating of alcohol **212** with sodium hydride in − 10 °C cooled tetrahydrofuran leads to the formation of sultam **213** in 75% yield (**Scheme 81**).

A series of benzoxathiazepine-1,1-dioxides **215** has been synthesized using a one-pot multicomponent reaction.[76] Treatment of 2-fluoro sulfamides **214** with oxiranes in boiling dioxane for 3 days leads to target compounds **215** in good and high yields (**Scheme 82**).

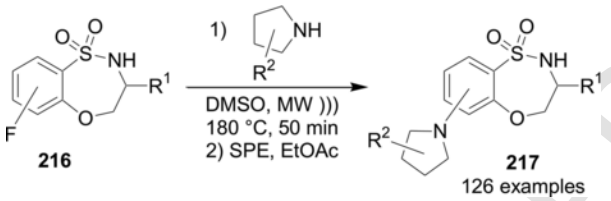
A microwave-assisted intermolecular S_NAr interaction of fluorobenzo[1,4,5] 1,1-dioxides **216** with substituted pyrroles was explored by Rolfe et al. during the development of a 126-member library of 1-pyrrolyl-benzo[1,4,5] 1,1-dioxides **217**[77] (**Scheme 83**).



212 213

Scheme 81

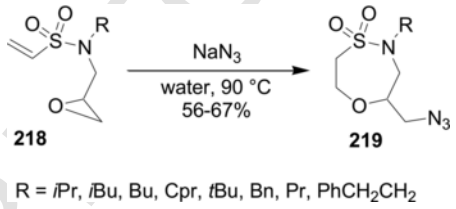
Scheme 82



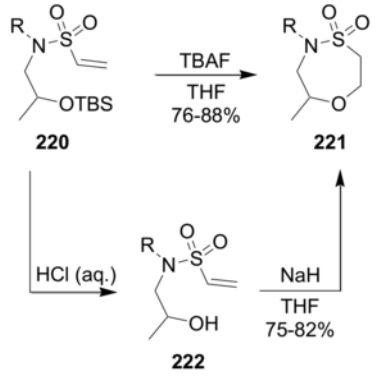
Scheme 83

Wang et al. have developed two tandem reaction protocols starting from one starting material—vinyl epoxysulfamide **218.**[78] Intermolecular epoxide ring-opening by sodium azide followed by an intramolecular 7-*endo*-trig oxa-Michael addition reaction and formation of corresponding azidomethyl-substituted 1,4,5-thiazepane 1,1-dioxides **219** (**Scheme 84**).

Seven-membered sultam derivatives **221** were conveniently synthesized via intramolecular Michael additions and an improved vinyl sulfonamide Baylise-Hillman reaction.[79] The authors have explored two different cyclization pathways for the oxa-Michael reaction (**Scheme 85**).



Scheme 84



Scheme 85

15 Systems containing at least one not N, O, or S heteroatom

Diemer et al. have investigated the cysteine selenosulfide (SetCys) redox behavior in protein chemical synthesis.[80] The oxidized form of SetCys **223** contains 1,2,5-thiaselenazepane ring (see **Scheme 86**). The authors have implemented the SetCys unit to execute the modular and consequent building of polypeptides. The synthesis of cyclic hepatocyte growth factor variants with biological activity have been performed.

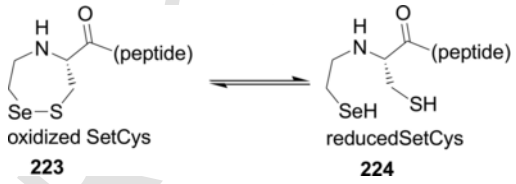
Tanini with co-authors, have described rongalite-promoted *on water* synthesis of functionalized tellurides via the reaction of sodium telluride with electrophiles.[81] Authors have used the reaction of elemental tellurium (1 eq.) with hydroxymethanesulfinate (aka rongalite) (2.5 eq.) in the presence of sodium hydroxide (5 eq.) at 90 °C under ultra-sound irradiation for 2 h in the water for the production of sodium telluride (**Scheme 87**). Then, the reaction mixture was treated with an excess (1.7 eq.) of 2-[(benzyloxy)methyl]thiirane, which leads to the formation of 3,6-bis[(benzyloxy)methyl]-1,4,5-telluradithiepane **225** in 48% yield.

The thiol peroxidase-like activity of a series of novel functionalized tellurium-containing catalysts has been investigated in the work of Tanini et al.[82] One of the studied Te-containing compounds was dithiatellurepane **226** (**Scheme 88**). The catalytic activity of compound 19-3-1 is much lower than on acyclic tellurides, which is quite surprising compared to what was previously observed on cyclic selenides. Synthesis of **226** was started from the reaction of elemental tellurium with $LiEt_3BH$ in tetrahydrofuran, which generates lithium telluride.[83,84] Further, reaction with methyl thiirane in THF at ambient temperature for 12 h leads to the target 2,6-dimethyl-1,4,5-dithiatellurepane **226**.

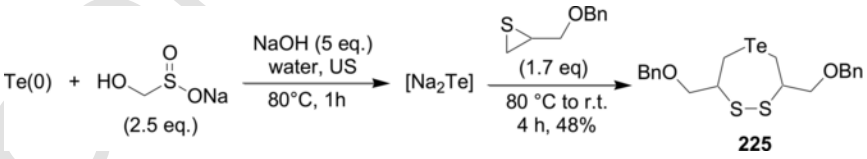
Jie with co-workers have studied addition reactions with an active six-membered phosphane/borane **227.**[85] The reaction of **227** with dimethyl acetylene dicarboxylate in dichloromethane leads to the formation of **228** as a pale yellow solid in 62% yield (**Scheme 89**). Next, a toluene solution of compound **228** was stirred at 50 °C for 20 h, giving 1,2,5-oxaboraphosphepine **229** as pale yellow crystals in 57% yield.

Alaoui-Jamali, with co-authors, patented a raw of purines with 1,2,5-diselenazepane moiety **230–232** as potent substances for cancer treatment[86] (see **Scheme 90**).

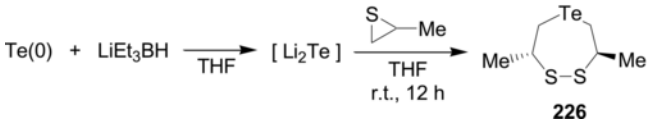
Cargoët et al. have investigated the catalytic activity of *N*-alkyl diselenides **234, 235,** and **238** in thioester − thiol exchange reaction and bis(2-sulfanylethyl)amido (SEA) mediated ligation.[87] Synthesis of 5-(3-hydroxypropyl)-1,2,5-diselenazepan-5-ium trifluoroacetate **234** was performed via alkylation of 1,2,5-diselenazepane trifluoroacetate **233** with bromopropanol in the presence of cesium hydroxide and 4 Å molecular sieves (MS) in DMF. Reaction mixture was stirred for 20 h at room temperature. The final product **234** was separated in only 4.5% yield (**Scheme 91**).



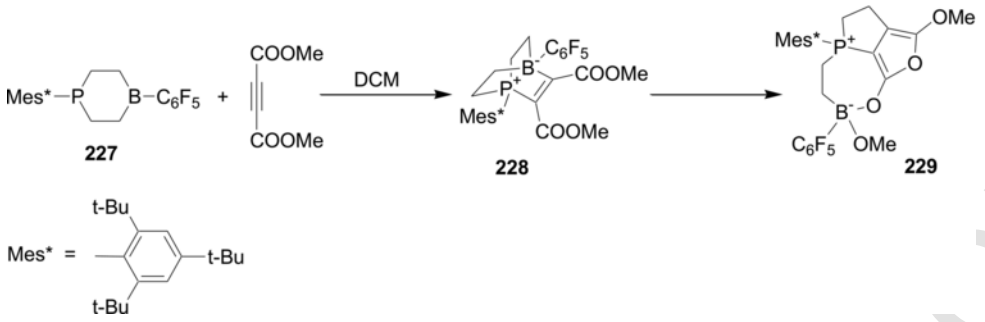
Scheme 86



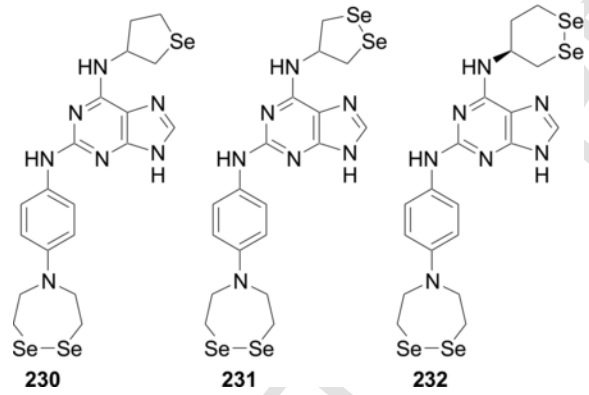
Scheme 87



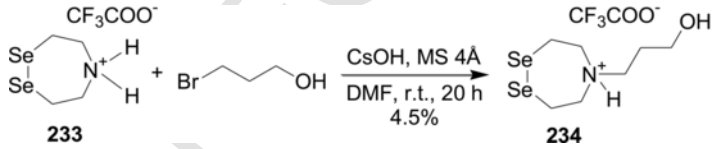
Scheme 88



Scheme 89



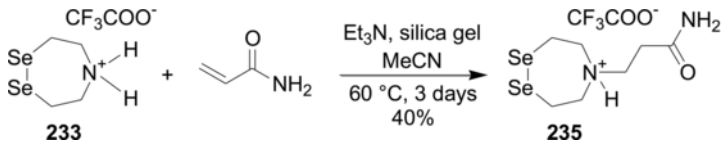
Scheme 90



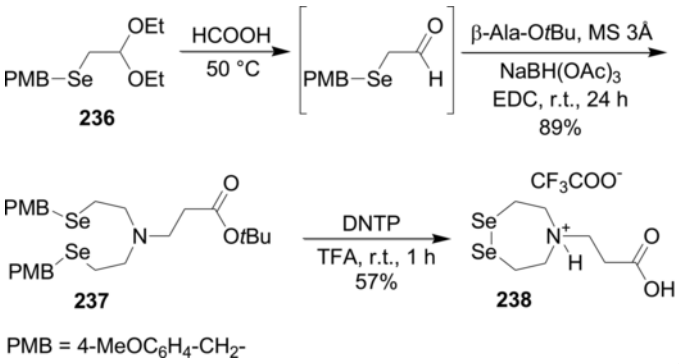
Scheme 91

Synthesis of **235** was performed via the interaction of 1,2,5-diselenazepane trifluoroacetate **233** with acrylamide in acetonitrile (**Scheme 92**). Silica gel and triethylamine were added to the mixture and the resulting suspension was stirred at 60 °C. The yield of purified fraction of the trifluoroacetate salt of 5-(2-carboxamidoethyl)-1,2,5-diselenazepan-5-ium **235** was 40%.

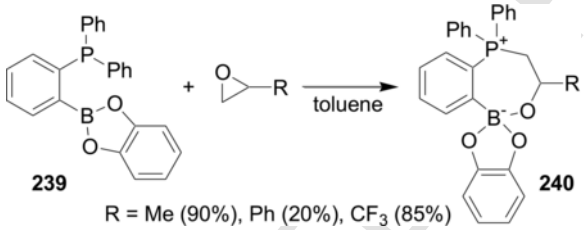
Selenide **236**, protected with *p*-methoxybenzyl (PMB) group, under the action of formic acid at 50 °C, produces aldehyde, which was involved in the reaction with β-alanine *tert*-butyl ester hydrochloride without separation (**Scheme 93**). The reaction was taken in 1,2-dichloroethane (EDC) in the presence of 3 Å molecular sieves and sodium triacetoxyborohydride. Next reaction of the amine **237** with a solution of 2,2′-dithiobis(5-nitropyridine) (DTNP) in trifluoroacetic acid under stirring at room temperature for 1 h leads to the formation of 5-(2-carboxyethyl)-1,2,5-diselenazepan-5-ium trifluoroacetate **238** in 57% yield.



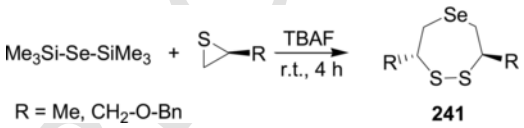
Scheme 92



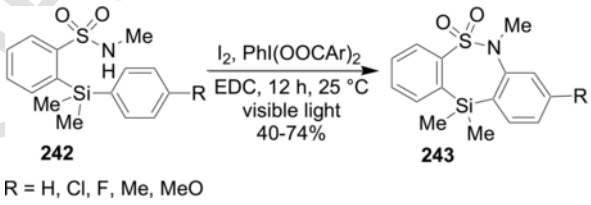
Scheme 93



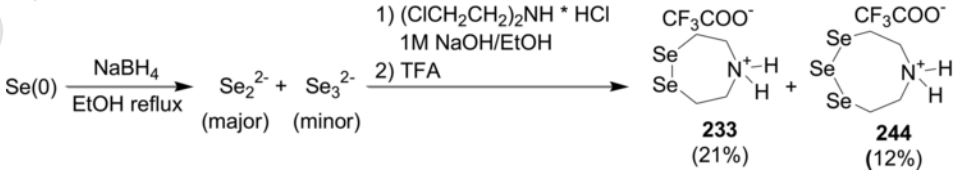
Scheme 94



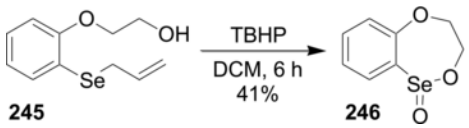
Scheme 95



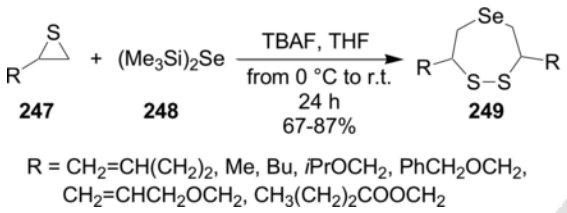
Scheme 96



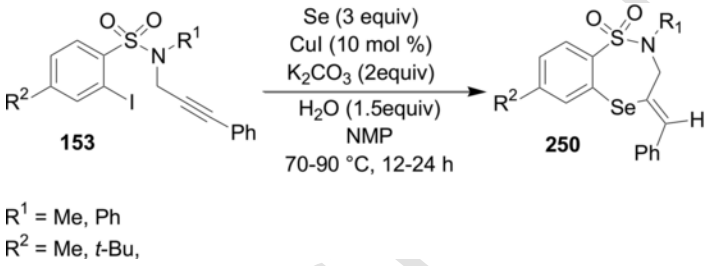
Scheme 97



Scheme 98



Scheme 99



Scheme 100

Krachko and co-authors have described the reaction of ring-opening of epoxides mediated by frustrated Lewis pairs (FLPs), particularly the reaction of 2-methyloxirane, 2-phenyloxirane, and 2-(trifluoromethyl)oxirane with *o*-phenylene-bridged FLP **240.**[88] In general, a toluene solution of corresponding oxirane was added dropwise to a solution of **239** in toluene at room temperature (**Scheme 94**). In the case of methyl- and phenyl-substituted oxiranes, the reaction mixture was allowed to stir at room temperature for 72 and 24 h, respectively. Whereas in the case of 2-(trifluoromethyl)oxirane, the mixture was heated at 70 °C for 72 h. Yield is high for methyl and trifluoromethyl-substituted oxiranes, whereas 2-phenyloxirane produces the target product in only 20% yield.

Tanini et al. have synthesized 1,2,5-dithiaselenepanes **241** exploiting the reactivity of bis(trimethylsilyl)selenide.[89] Reaction with substituted thiiranes leads to disubstituted selenides, however, the increase of the reaction time and addition of tetrabutylammonium fluoride leads to mild oxidation of mercapto groups and formation of the target 1,2,5-dithiaselenepanes **241** (**Scheme 95**). Authors have studied an antioxidant catalytic activity of these compounds in the reaction of hydrogen peroxide with dithiothreitol. It was found that the more hindered dithiaselenepane with benzyloxymethyl groups showed a lower catalytic efficiency than 3,7-dimethyl-1,2,5-dithiaselenepane.

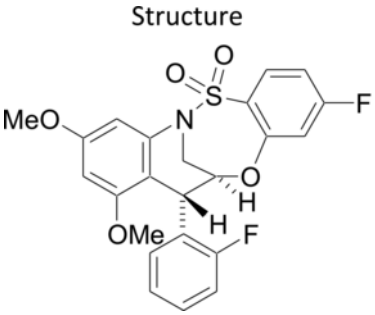
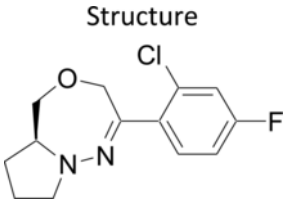
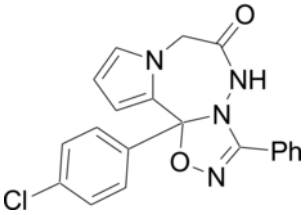
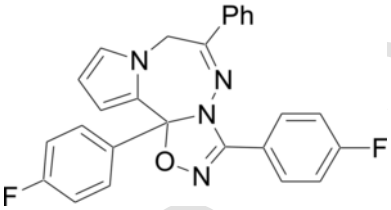
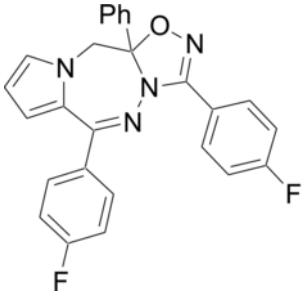
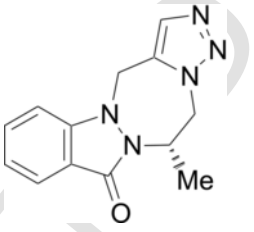
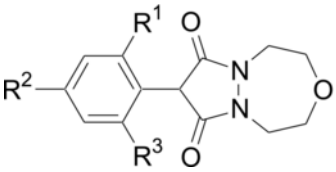
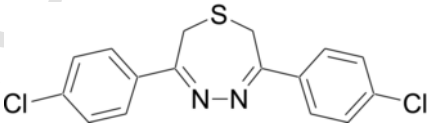
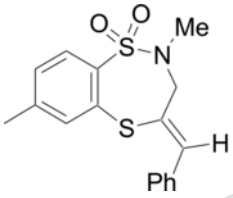
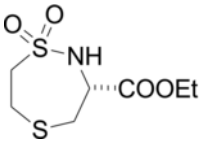
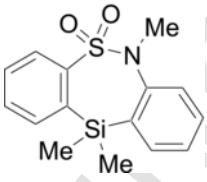
Martinez et al. have described photochemical catalytic amination of arenes under benign iodine catalysis in the presence of visible light as the initiator.[90] Authors have expanded the scope of the reaction and obtained in medium and good yield numerous silyl-tethered heterocyclic derivatives **243** from sulfamides **242** (**Scheme 96**).

1,2,5-Diselenazepan-5-ium trifluoroacetate **233** is a versatile precursor to bis(2-selenylethyl)amido peptides.[91] Free selenium can be reduced to sodium borohydride via refluxing in ethanol.[92] The next stage of the synthesis is the treatment of the resulting diselenide dianion Se_2^{2-} with bis(2-chloroethyl)amine hydrochloride in the presence of sodium hydroxide in ethanol (**Scheme 97**). The target 1,2,5-diselenazepane was isolated as trifluoroacetate salt in 21% yield. The author have noted the formation of the trifluoroacetate salt of 1,2,3,6-triselenazocane 19–21 in 12% yield.

Tripathi et al. have explored 2-phenoxyethanol derived diselenide for the synthesis of a seven-membered seleninate.[93] A solution of allyl selenide **245** in dichloromethane was mixed with *tert*-butyl hydroperoxide (TBHP) (**Scheme 98**). The reaction mixture was stirred for 6 h at room temperature. The target **246** was obtained in 41% yield.

Capperucci et al. have investigated the reaction of substituted thiiranes **247** with bis(trimethylsilyl) selenide **248** different leads to 3,7-disubstituted-1,2,5-trithiepanes **249.**[24] The synthesis was performed in tetrahydrofuran at 0 °C with next heating to room temperature. Tetrabutylammonium fluoride (TBAF) was used as a catalyst (**Scheme 99**).

Table 2 X-ray crystallographic studies of compounds.

Structure	*References*	*Structure*	*References*
	67		10
	11		11
	11		18
	28		94
	52		53
	90		

A novel and Cu(I)-catalyzed one-pot regio- and stereospecific synthesis of benzo[1,5,2]thiaselenazepine 1,1-dioxides **250** by cyclization of functionalized propynamides **153** with elemental selenium has been developed[52] (**Scheme 100**).

16 X-ray crystallography

Structure of the compounds listed in **Table 2** have been resolved via X-ray diffraction studies. In the case of 3,6-di(*p*-chlorophenyl)-2,7-dihydro-1,4,5-thiadiazepine,authors have analyzed the crystal structure interms of Hirshfeld surface analysis.[94] Fingerprint plots were used for visualizing and exploring of title compound for quantifying intermolecular interactions in crystal lattice.

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