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SYNTHESIS AND CHEMICAL TRANSFORMATIONS OF BENZOXAZEPINES[#]

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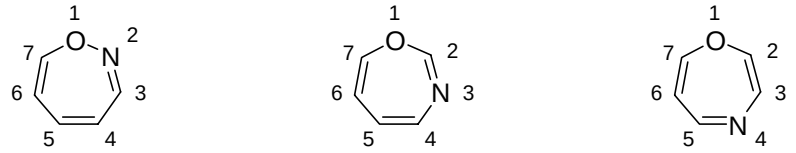
Abstract - This review describes synthetic procedures for the preparation of all the known benzocondensed derivatives of the 1,2-, 1,3- and 1,4-oxazepines. Examples for the most important chemical transformations of some benzoxazepine groups providing their useful derivatives have also been included. Owing to the huge number of papers in this field, it is not the aim of this review article to list and discuss all the papers published in the chemical literature.

1. INTRODUCTION

Benzoxazepines are the benzocondensed derivatives of the three isomeric oxazepine parent compounds (Scheme 1).

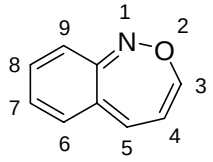


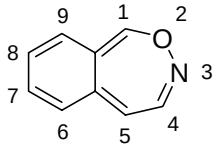
Scheme 1

Theoretically ten benzoxazepine isomers can be derived from these three oxazepine isomers. Four possible benzoxazepines, *viz.* 1,2-, 2,1-, 2,3- and 3,2-benzoxazepines are derived from the 1,2-oxazepine. However, neither the 1,2-benzoxazepine nor its derivatives have hitherto been described in the literature. All three possible benzoxazepines, the 1,3-, 3,1- and 2,4-benzoxazepines, originating from the 1,3-oxazepine are known compounds. Three possible benzocondensed derivatives of the 1,4-oxazepine, *viz.*

1,4-, 4,1- and 1,5-benzoxazepines are known substances. The skeletons of all known benzoxazepine isomers, together with the numbering of their atoms, are illustrated in Scheme 2.

Except for the 1,3-benzoxazepine and 3,1-benzoxazepine, these basic structures shown in Scheme 2 are not known as particular substances. For this reason, only the derivatives of the other parent structures have hitherto been described in the chemical literature. There are no general methods for the preparation of these structurally related compounds. As a consequence, special synthetic procedures should be developed for each isomeric group of benzoxazepines. In this review article the most relevant methods are summarized. Well known chemical transformations of some groups of benzoxazepines will also be discussed with the help of adequate examples.


2,1-benzoxazepine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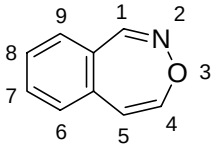
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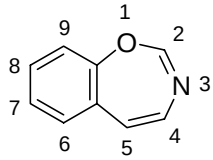
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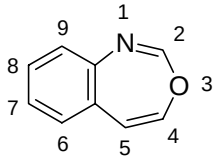
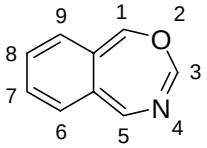
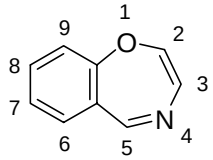
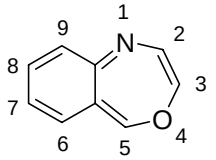
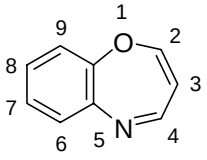

3,1-benzoxazepine


2,4-benzoxazepine


1,4-benzoxazepine


4,1-benzoxazepine

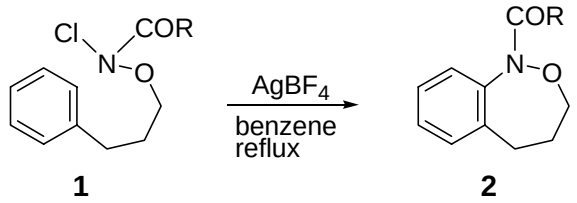

1,5-benzoxazepine

Scheme 2

2. SYNTHESIS OF BENZOCONDENSED 1,2-OXAZEPINES

2.1. 2,1-Benzoxazepines

Only few 1,3,4,5-tetrahydro-2,1-benzoxazepine derivatives **2** have been published in the literature.[1,2] These compounds were obtained by the ring closure of *N*-chloro hydroxamates **1** with silver tetrafluoroborate in anhydrous ether (Scheme 3).



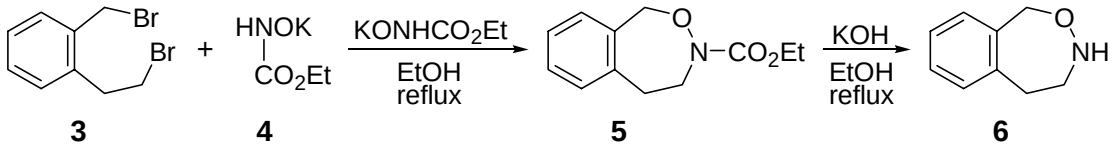
1 **2**

R: Me, Ph

Scheme 3

2.2. 2,3-Benzoxazepines

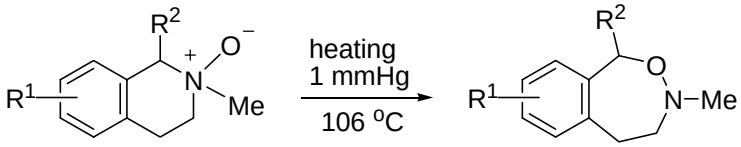
The 1,3,4,5-tetrahydro-2,3-benzoxazepine (**6**) itself was synthesized by Pifferi *et al.*[3] in 1971. Condensation of *o*-bromomethylphenethyl bromide (**3**) with the potassium salt of *N*-hydroxyurethan (**4**) yielded 3-carbethoxy-1,3,4,5-tetrahydro-2,3-benzoxazepine (**5**) which was then hydrolyzed to give 1,3,4,5-tetrahydro-2,3-benzoxazepine (**6**) (Scheme 4).



3 **4** **5** **6**

Scheme 4

A series of 1,3,4,5-tetrahydro-2,3-benzoxazepines **8** have been synthesized by a thermal transformation of 1-aryl-1,2,3,4-tetrahydroisoquinoline *N*-oxides **7.** This ring expansion may start with a homolytic cleavage of the C-1-N bond resulting in the formation of a diradical capable of a C-O bond formation providing a seven-membered ring system (Scheme 5).[4,5]



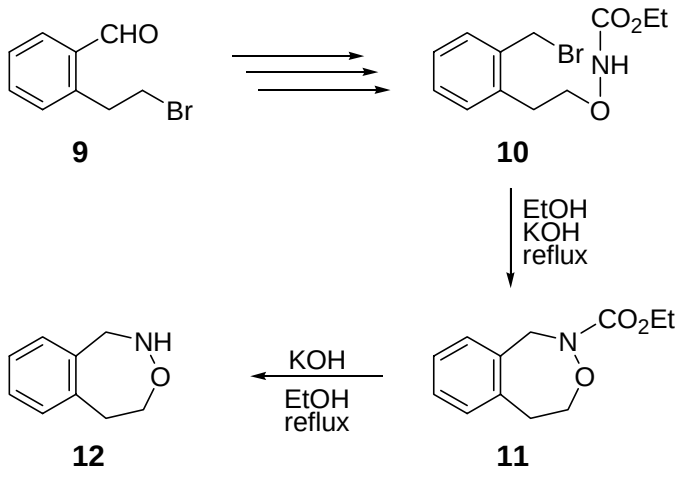
7 **8**

Scheme 5

2.3. 3,2-Benzoxazepines

Hydroxylamine derivative **10** was prepared from *o*-(2-bromoethyl)benzaldehyde **9** *via* several steps. Cyclization of compound **10** afforded 2-ethoxycarbonyl-1,2,4,5-tetrahydro-3,2-benzoxazepine (**11**) which

was then hydrolized with potassium hydroxide to give 1,2,4,5-tetrahydro-3,2-benzoxazepine (**12**) (Scheme 6).[3]

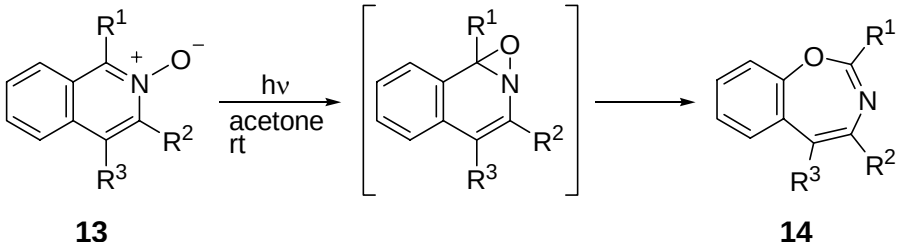


Scheme 6

3. SYNTHESIS OF BENZOCONDENSED 1,3-OXAZEPINES

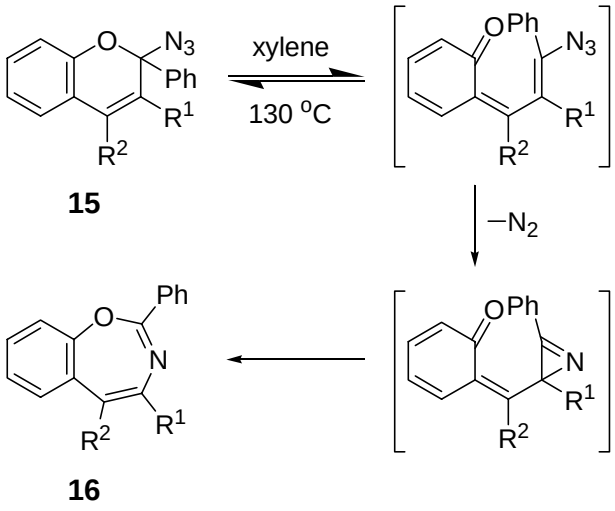
3.1. 1,3-Benzoxazepines

Various procedures have been worked out for the preparation of 1,3-benzoxazepines. A generally used method is the photoisomerization of isoquinoline *N*-oxides **13** to afford *e.g.* 2,4,5-trisubstituted 1,3-benzoxazepines **14** (Scheme 7).[6-9] The parent 1,3-benzoxazepine (*cf.* Scheme 2) itself was prepared by this method, too.[7]



Scheme 7

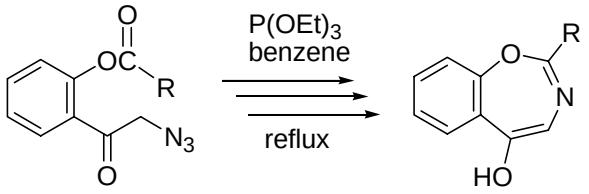
Desbene and Cherton[10] synthesized 2,4,5-trisubstituted 1,3-benzoxazepines **16** by the thermal rearrangement of 2-azido-2*H*-chromenes **15** (Scheme 8).



15 **16**

Scheme 8

2-Substituted 5-hydroxy-1,3-benzoxazepines **18** have been synthesized starting from *o*-acyloxyphenyl azides **17** *via* several steps (Scheme 9).[11]

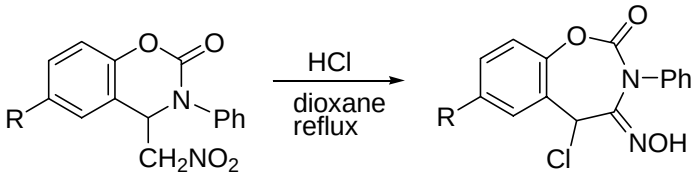


17 **18**

R: H, Me, Pr, Ph

Scheme 9

2,4,5-Trihydro-1,3-benzoxazepine derivatives **20** have been prepared by Katritzky *et al.*[12] by the ring enlargement of 3,4-dihydro-1,3-benzoxazin-2-ones **19** under acidic conditions (Scheme 10).



19 **20**

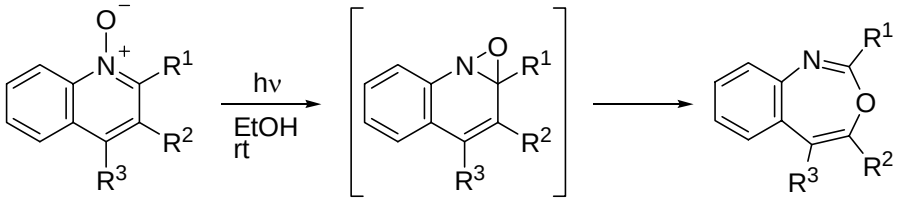
R: H, Cl

Scheme 10

Most recently, as a special polycyclic ring system, indole condensed derivatives of 1,3-benzoxazepines were obtained by the cyclization of 6-nitro-spirobenzopyrans.[13]

3.2. 3,1-Benzoxazepines

A general procedure for the preparation of 3,1-benzoxazepines **22** is the photoisomerization of quinoline *N*-oxides **21** in ethanolic solution (Scheme 11).[7,14-18] The utilization of this method makes possible the synthesis of numerous substituted 3,1-benzoxazepines.

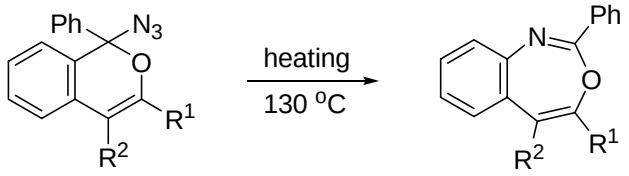


21 **22**

R^1: H, Me, Ph; R^2: H, Me; R^3: H, Me

Scheme 11

Thermal rearrangement of 1-azidoisochromenes **23** in xylene solution provided 2,4,5-trisubstituted 3,1-benzoxazepines **24** (Scheme 12).[19]



23 **24**

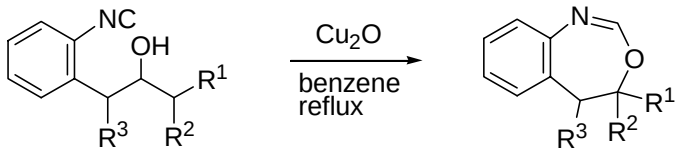
R^1: H, Ph; R^2: H, Ph

Scheme 12

4,5-Dihydro-3,1-benzoxazepines **26** were obtained by the Cu_2O catalyzed ring closure of *o*-(β-hydroxyalkyl)phenyl isocyanides **25** in hot benzene (Scheme 13).[20-22]

A special procedure for the preparation of 4,5-dihydro-3,1-benzoxazepines **30** has been described by Capozzi *et al.*[23] *N*-Benzoyl-*o*-allylaniline derivative **27** was allowed to react with methyl(bismethylthio)sulphonium hexachloroantimonate **28** in dichloromethane at 0 °C to afford the 3,1-

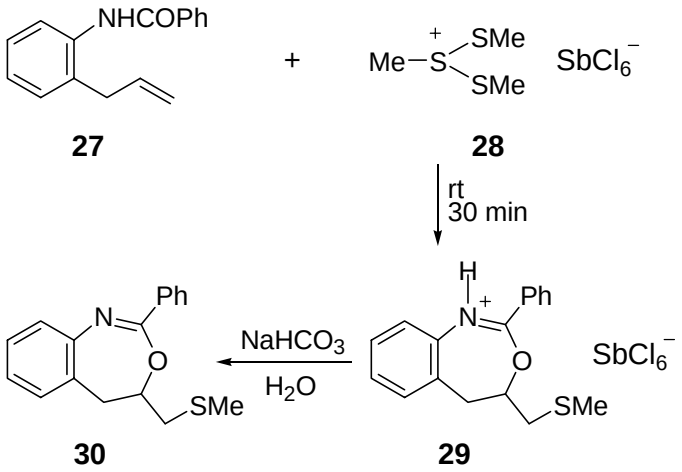
benzoxazepinium hexachloroantimonate **29**. Compound **29** provided 4,5-dihydro-4-(methylthio)methyl-2-phenyl-3,1-benzoxazepine (**30**) on treatment with aqueous sodium bicarbonate solution (Scheme 14).



25 **26**

R^1: H, Me; R^2: Me, Et; R^3: H, Me

Scheme 13

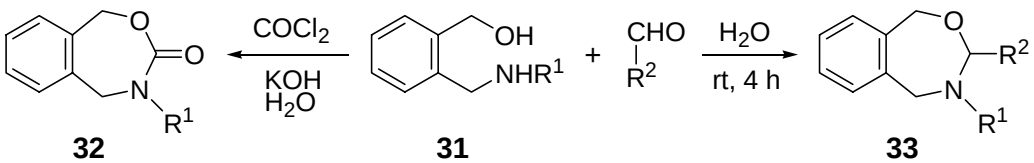


27 **28** **29** **30**

Scheme 14

3.3. 2,4-Benzoxazepines

2,4-Benzoxazepines belong to the less known benzocondensed derivatives of the 1,3-oxazepine (Scheme 1). 4,5-Dihydro-2,4-benzoxazepines **32** were obtained by the reaction of (*o*-aminomethyl)benzyl alcohols **31** with phosgene under alkaline reaction conditions (Scheme 15).[24] 1,3,4,5-Tetrahydro-2,4-benzoxazepines **33** can also be prepared from alcohols **31** by their reaction with aldehydes on acidic treatment (Scheme 15).[24]



32 **31** **33**

R^1: COMe, COEt; R^2: H, Pr

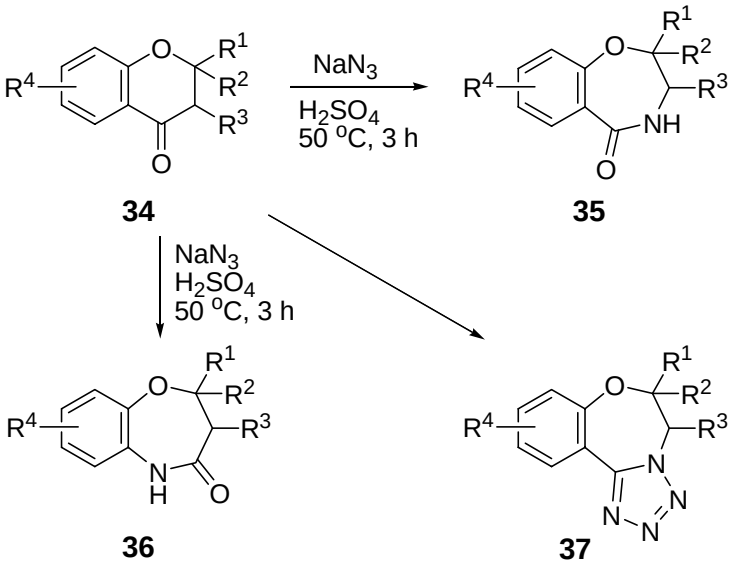
Scheme 15

A special group of 2,4-benzoxazepines, *viz.* 5*H*,7*H*-pyrazolo[1,5-*d*][2,4]benzoxazepin-7-ones were synthesized by the reaction of azine ylides with phthalic anhydride.[25]

4. SYNTHESIS OF BENZOCONDENSED 1,4-OXAZEPINES

4.1. 1,4-Benzoxazepines

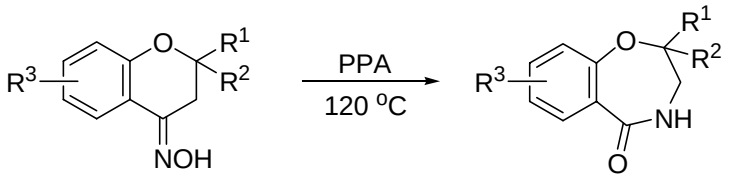
1,4-Benzoxazepines are the most frequently studied benzoxazepine isomers. It may be a consequence of their numerous bioactivities, *viz.* antiinflammatory,[26] antihistaminic,[27,28] PGE_2 antagonist,[29] anti-ischemic,[30,31] neuroprotective,[32] tyrosine kinase inhibitory,[33,34] etc. effects. For this reason, these benzoxazepines are useful substances in the drug research which stimulated the efforts to develop various synthetic procedures for their economic preparation. 2,3-Dihydro-1,4-benzoxazepin-5(4*H*)-ones **35** comprise a well known group of the 1,4-benzoxazepine derivatives. One of the most common methods for the preparation of 1,4-benzoxazepines **35** is the Schmidt reaction of the appropriate 4-chromanones **34**. 4-Chromanones **34** are allowed to react with *in situ* liberated hydrazoic acid under strongly acidic conditions to give 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **35** (Scheme 16).[35-51] In some cases, 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **36** and/or tetrazoles **37** were detected or isolated as by-products (Scheme 16).[39-41,46-48]



R^1: H, Me, Ph; R^2: H, Me; R^3: H, Ph; R^4: Me, alkoxy

Scheme 16

Another convenient method for the preparation of compounds **35** is the Beckmann rearrangement of the oximes **38** of 4-chromanones.[52-55] Compounds **38** are treated with polyphosphoric acid to provide 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **35** (Scheme 17). On the basis of parallel experimental results, it can be concluded that the Schmidt reaction of the 4-chromanones and the Beckmann reaction of their oximes provide the same 1,4-benzoxazepine derivatives.



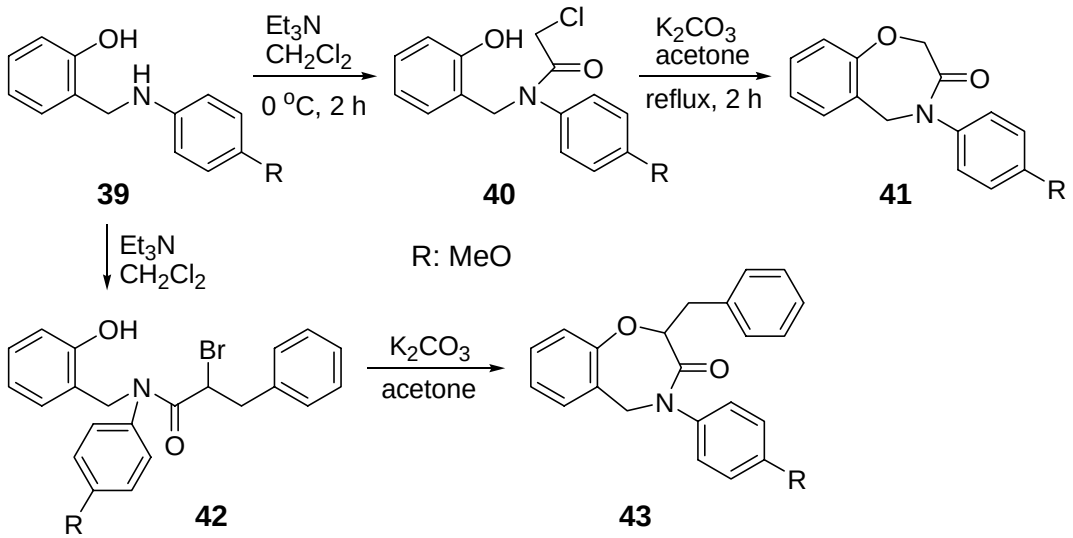
38 **35**

R^1: H, Me, Ph; R^2: H, Me; R^3: alkyl, alkoxy

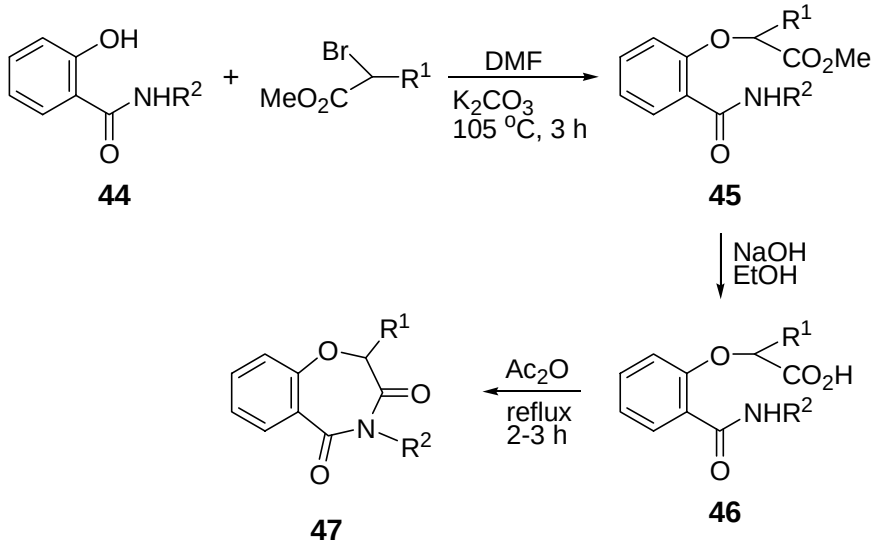
Scheme 17

1,4-Benzoxazepines have been synthesized starting from salicylaldehyde. Salicylaldehyde was allowed to react wirh *p*-substituted anilines in hot ethanol to give imines which were then reduced by sodium borohydride in the same solution at room temperature to afford compounds **39** as reasonable starting materials for the preparation of 1,4-benzoxazepin-3-ones. In case compound **39** (R = MeO) was reacted with chloroacetyl chloride, its *N*-chloroacetyl derivative **40** was obtained which gave 4-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-one (**41**) on ring closure with potassium carbonate (Scheme 18). However, if compound **39** was treated with 2-bromo-3-phenylpropionyl chloride, bromoamide **42** was yielded which provided 4-aryl-2-benzyl-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-ones **43** on alkaline cyclization (Scheme 18).[56]

2,4-Disubstituted 2,3,4,5-tetrahydro-1,4-benzoxazepin-3,5-diones **47** have been synthesized by Kwiecien[57-59] starting from salicylamide derivatives **44**. Compounds **44** were allowed to react with methyl bromoacetate to afford esters **45** which were saponified to yield carboxylic acids **46**. Ring closure of compounds **46** gave the 1,4-benzoxazepin-3,5-dione derivatives **47** (Scheme 19).

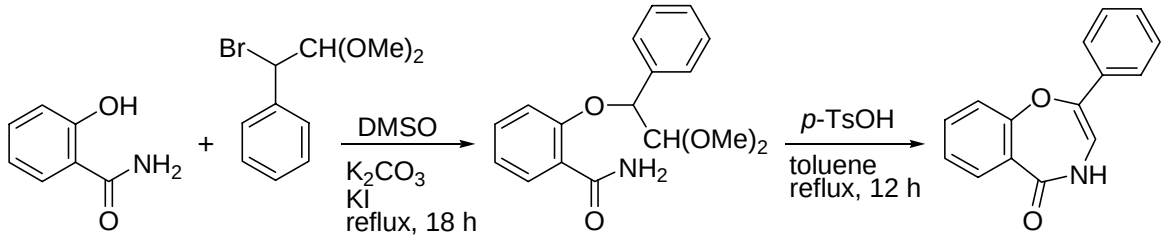


Scheme 18



Scheme 19

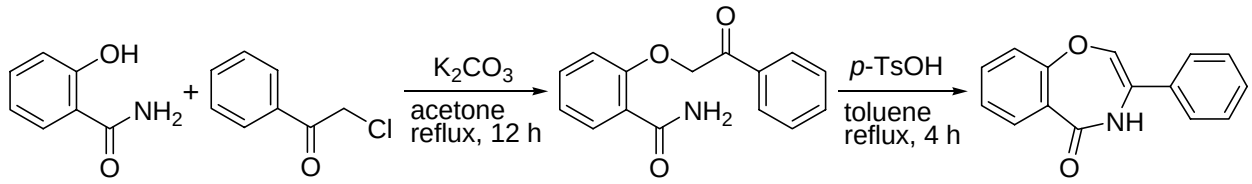
2-Phenyl-1,4-benzoxazepin-5(4*H*)-one (**51**) was synthesized by Kaye *et al.*[60,61] starting from salicylamide (**48**). Compound **48** was treated with bromoacetal **49** to afford *o*-(2,2-dimethoxy-1-phenylethyl)salicylamide (**50**), ring closure of which gave 1,4-benzoxazepine **51** (Scheme 20).



48 **49** **50** **51**

Scheme 20

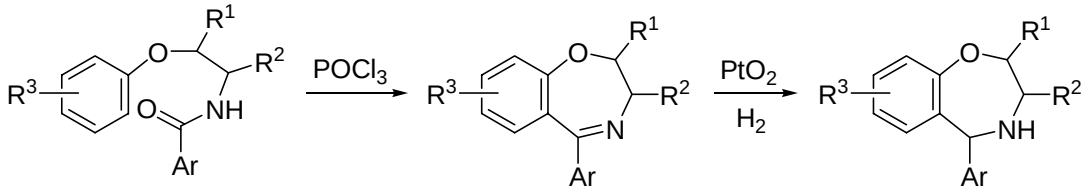
3-Phenyl-1,4-benzoxazepin-5(4*H*)-one (**54**) has also been synthesized strating from salicylamide (**48**). Salicylamide **48** was alkylated with phenacyl chloride (**52**) to afford 2-phenacyloxy benzamide (**53**), acid catalyzed ring closure of which yielded 3-phenyl-1,4-benzoxazepin-5(4*H*)-one (**54**) (Scheme 21).[62]



48 **52** **53** **54**

Scheme 21

5-Aryl-2,3-dihydro-1,4-benzoxazepines **56** have been prepared by the Bischler-Napieralski reaction of benzamides **55** (Scheme 22).[63-65] Benzoxazepines **56** gave 2,3,4,5-tetrahydro-1,4-benzoxazepines **57** on hydrogenation in the presence of Adams platinum catalyst (Scheme 22).

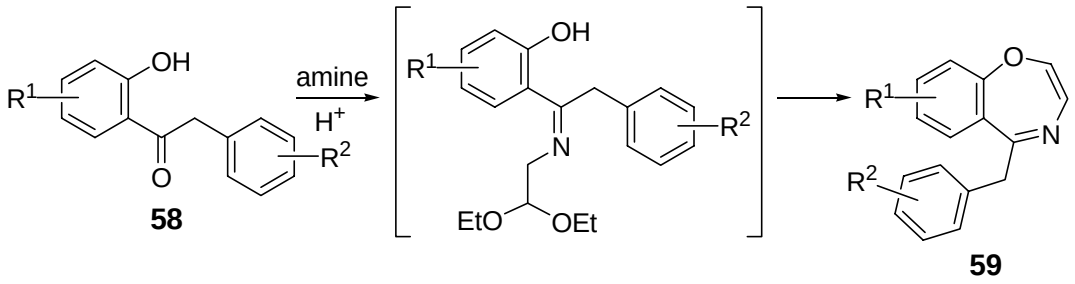


55 **56** **57**

R^1: H, Me; R^2: Me, Et, *i*-Pr; R^3: H, Me, alkoxy, Cl

Scheme 22

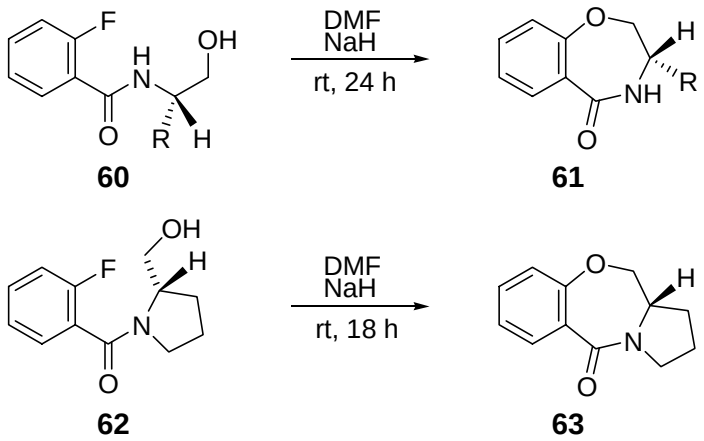
5-Benzyl-1,4-benzoxazepines **59** were prepared starting from 2-hydroxydeoxybenzoins **58**. Compounds **58** were allowed to react with aminoacetaldehyde diethyl acetal to afford Schiff bases, ring closure of which provided 5-benzyl-1,4-benzoxazepines **59** (Scheme 23).[66]



R^1: MeO, Br; R^2 = MeO, Cl, Br

Scheme 23

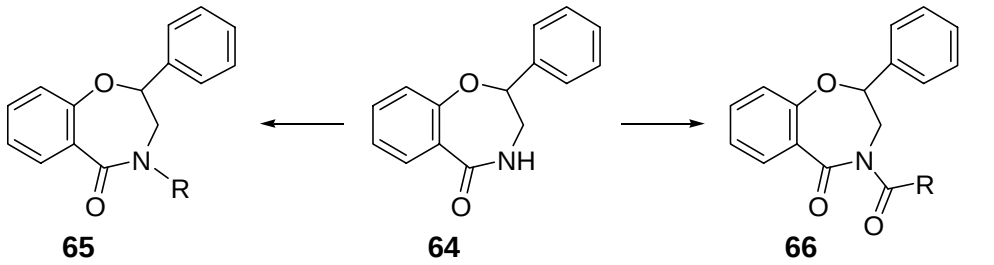
Only few optically active 1,4-benzoxazepines have been synthesized. Schultz *et al.*[67-69] prepared 3-substituted 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **61** by the ring closure of fluorobenzamides **60** in dry dimethylformamide in the presence of sodium hydride (Scheme 24). This method was used for the synthesis of optically active tricyclic 1,4-benzoxazepines **63** by the cyclization of compounds **62** (Scheme 24). Hirschmann *et al.*[70] described the utilization of sugar scaffold to obtain 1,4-benzoxazepin-5-one.



Scheme 24

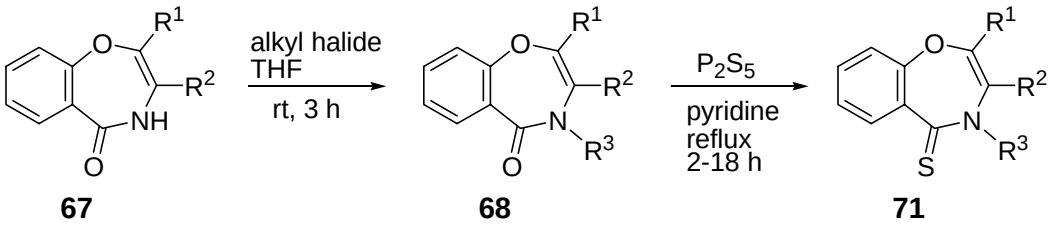
Several new substances were obtained by the *N*-alkylation and *N*-acylation of 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (**64**) (Scheme 25).[44,49,61] *N*-Alkylation of the 2-phenyl-2,3-diyhdro-1,4-benzoxazepin-5(4*H*)-one (**64**) has been achieved with alkyl halides in anhydrous dimethylformamide in the presence of sodium hydride to yield the appropriate *N*-alkyl derivatives **65** (Scheme 25).[44,49]

Compound **64** was acylated with carboxylic acid chlorides or anhydrides in the presence of base to give *N*-acylated derivatives **66** (Scheme 25).[49]

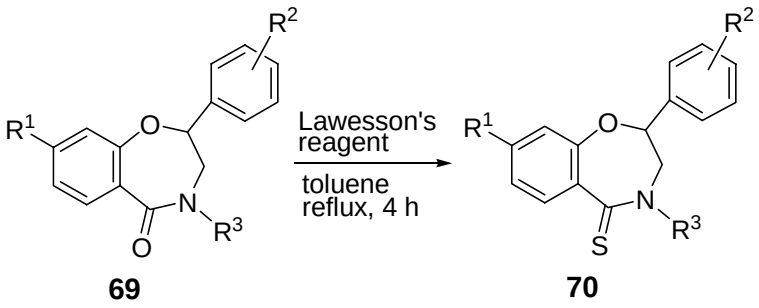


Scheme 25

Kaye *et al.*[61] synthesized *N*-alkylated 1,4-benzoxazepin-5(4*H*)-ones **68** by the reaction of 1,4-benzoxazepin-5(4*H*)-ones **67** with alkyl halides under alkaline conditions (Scheme 26).



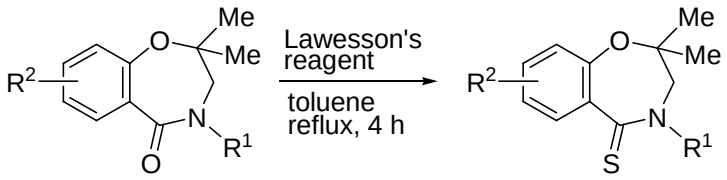
Scheme 26



Scheme 27

1,4-Benzoxazepin-5(4*H*)-ones **69** have been converted into their 5-thio derivatives **70** by various reagents. For example, when 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **69** were reacted with phosphorus pentasulfide, 2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-thiones **70** were obtained (Scheme 27).[44] This reagent was used by Kaye *et al.*[61] to convert 1,4-benzoxazepin-5(4*H*)-ones **68** into their 5-thio analogues **71** (Scheme 26).

The Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide][72] proved to be the most efficient reagent to transform amides into the appropriate thioamides. 2,2-Dimethyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **72** were allowed to react with Lawesson's Reagent in hot anhydrous toluene to afford their 5-thio derivatives **73** (Scheme 28).[47,49]

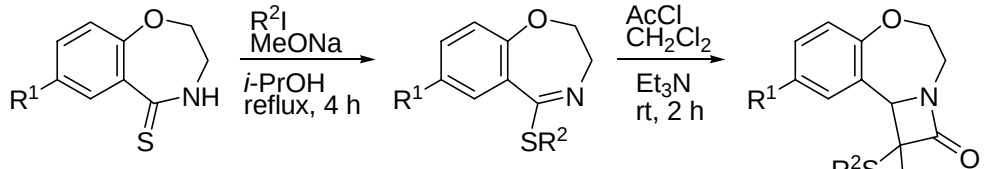


72 **73**

R^1: H, Me; R^2: H, Me, alkoxy

Scheme 28

2,3-Dihydro-1,4-benzoxazepin-5(4*H*)-thiones **74** proved to be convenient starting materials for the preparation of the β-lactam derivatives **76** of 1,4-benzoxazepines. Compounds **74** were first alkylated to yield thioimidates **75** which were then reacted with *in situ* generated ketenes to afford the β-lactams **76** (Scheme 29).[73]

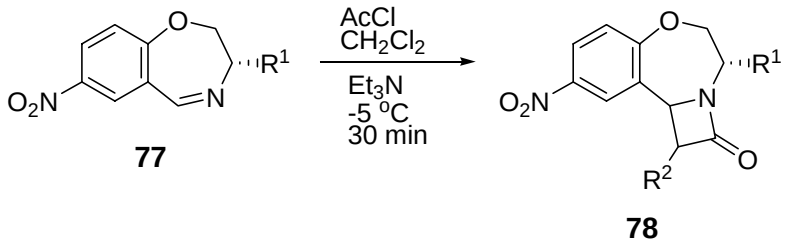


74 **75** **76**

R^1: H, Cl; R^2: Me, Et, *i*-Pr

Scheme 29

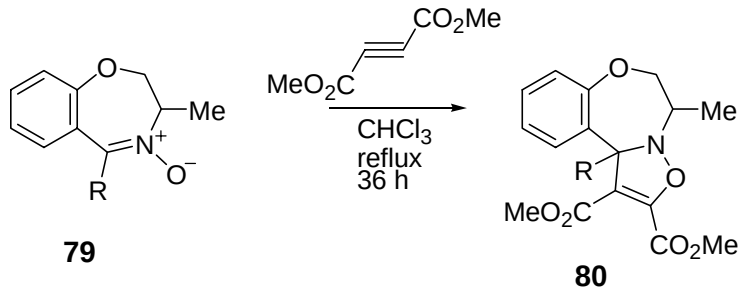
Optically active β-lactam derivatives **78** have been synthesized by Buttero *et al.*[74] by the [2+2] cycloaddition reaction of enantiomerically pure 1,4-benzoxazepines **77** with phenoxyacetyl or phthalimidoacetyl chloride (Scheme 30).



R^1: Me, *i*-Pr, Ph; R^2: PhO, phthalimido

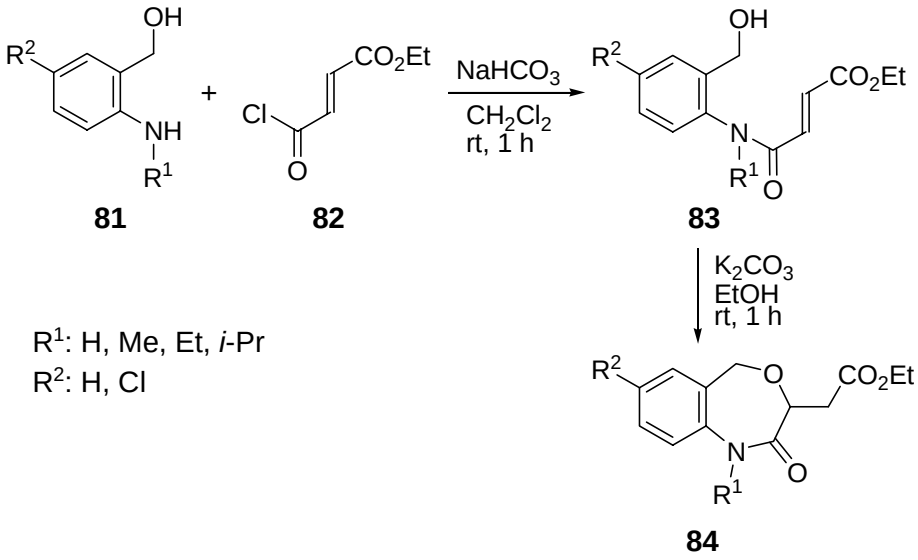
Scheme 30

Heaney *et al.*[75] synthesized tetrahydroisoxazolo[2,3-*d*][1,4]benzoxazepines **80** in high yields by the 1,3-dipolar cycloaddition of 1,4-benzoxazepine nitrones **79** with dimethyl acetylenedicarboxylate (Scheme 31).



R: Me, Ph

Scheme 31



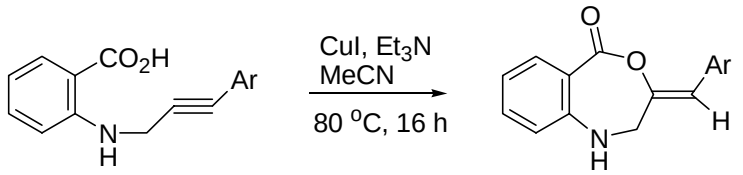
R^1: H, Me, Et, *i*-Pr
R^2: H, Cl

Scheme 32

4.2. 4,1-Benzoxazepines

Least studied benzocondensed derivatives of the 1,4-oxazepine are the 4,1-benzoxazepines. Nevertheless, several methods have been developed for the synthesis of their derivatives. 1,2,3,5-Tetrahydro-4,1-benzoxazepin-2-ones **84** were prepared starting from 2-aminobenzyl alcohols **81** which was first *N*-acylated with fumaric acid chloride monoethyl ester (**82**) to obtain the intermediates **83** ring closure of which afforded the desired 1,2,3,5-tetrahydro-4,1-benzoxazepin-2-ones **84** (Scheme 32).[76]

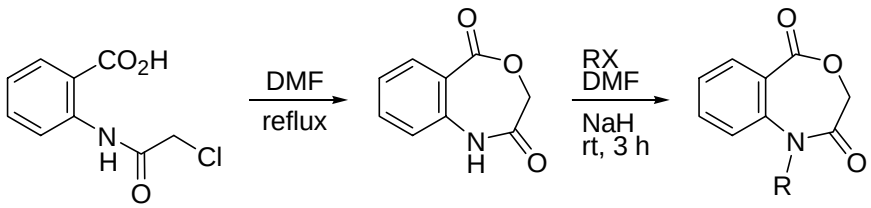
(*Z*)-3-Arylidene-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-ones **86** were synthesized by Chaudhuri and Kundu[77] by the cyclization of carboxylic acid **85** in the presence of cuprous iodide and triethylamine in acetonitrile solution (Scheme 33).



85 **86**

Scheme 33

1,2,3,5-Tetrahydro-4,1-benzoxazepin-2,5-dione (**88**) was obtained by the ring closure of *N*-chloroacetylanthranilic acid (**87**). Alkylation of compound **88** with alkyl halides in the presence of sodium hydride in anhydrous dimethylformamide provided its *N*-alkyl derivatives **89** (Scheme 34).[78,79]

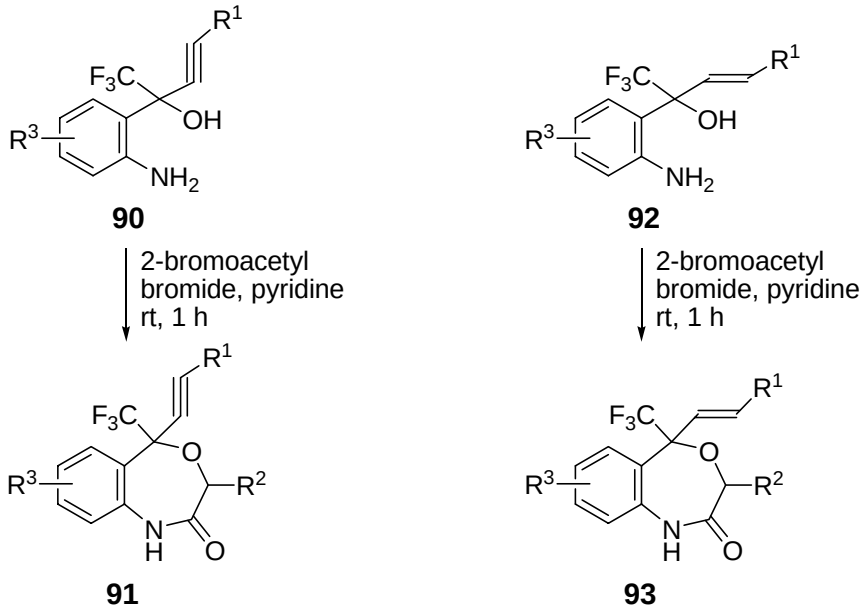


87 **88** **89**

R: alkyl, benzyl

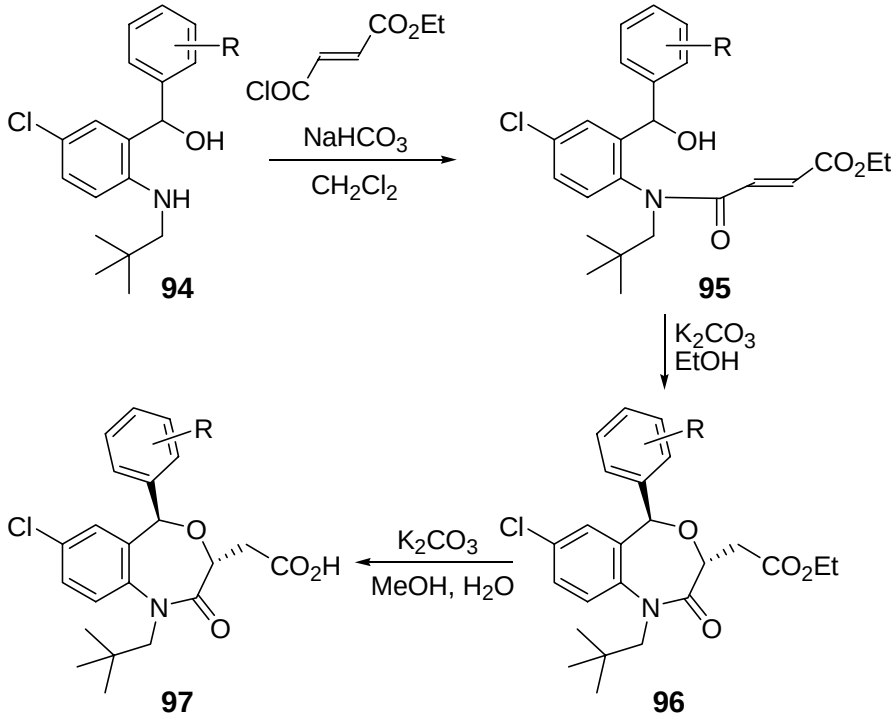
Scheme 34

Non-nucleoside reverse transcriptase inhibitor 4,1-benzoxazepines have been synthesized by Cocuzza *et al.*[80] Acetylenic aminoalcohols **90** were converted into 1,2,3,5-tetrahydro-4,1-benzoxazepin-2-ones **91** on treatment with bromoacetyl bromides (Scheme 35). Related *trans* olefinic aminoalcohols **92** gave similar 1,2,3,5-tetrahydro-4,1-benzoxazepin-2-ones **93** (Scheme 35) when cyclized with bromoacetyl bromides.



R^1: Et, *i*-Pr, Ph; R^2: H, Me, Et, Pr, *i*-Pr; R^3: F, Cl

Scheme 35

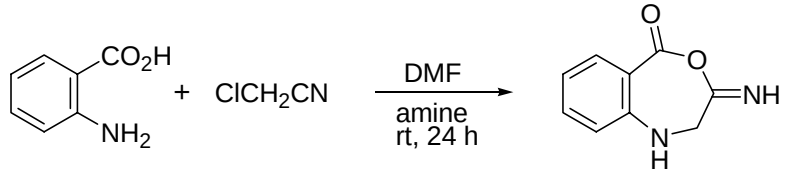


R: 2-Cl, 2-OMe, 2,3-$(OMe)_2$, 2,4-$(OMe)_2$

Scheme 36

Recently, optically active 4,1-benzoxazepine derivatives **97** with squalene synthase inhibitory and cholesterol biosynthesis inhibitory activities have been synthesized and tested by Miki *et al.*[81-84] Aminoalcohols **94** were allowed to react with fumaric acid chloride monoethyl ester to give amide **95**. Compounds **95** were cyclized to afford ethyl 4,1-benzoxazepin-3-acetates **96**. In this reaction the thermodynamically more stable 3,5-*trans*-diastereomers were formed which gave carboxylic acids **97** on saponification (Scheme 36).

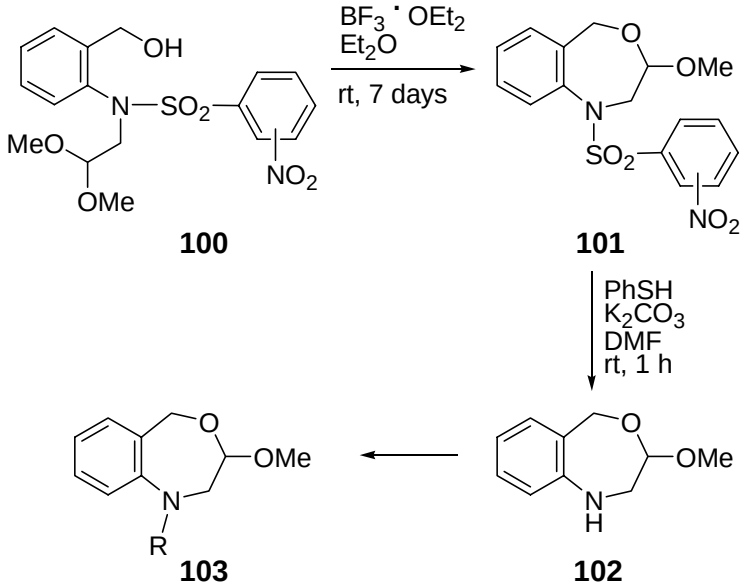
Mitchell and Hurley[85] synthesized 3-imino-2,3-dihydro-4,1-benzoxazepin-5(1*H*)-one (**99**) by the reaction of anthranilic acid (**98**) with chloroacetonitrile in the presence of *N*,*N*-diisopropylethylamine in dimethylformamide solution (Scheme 37).



98 **99**

Scheme 37

N-Substituted 3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines **103** were synthesized by the cyclization of alcohol derivatives **100** followed by the hydrolysis of intermediate **101** to produce 4,1-benzoxazepines **102**, *N*-acylation of which provided the target *N*-substituted 3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines **103** (Scheme 38).[86] Reaction of these 4,1-benzoxazepines with uracil and 5-fluorouracil has also been studied.[87]



100 **101** **102** **103**

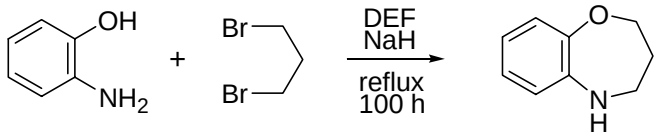
R: COPr, $COCF_3$, COPh

Scheme 38

4.3. 1,5-Benzoxazepines

1,5-Benzoxazepines are the second largest group of the benzoxazepines. The 2,3,4,5-tetrahydro-1,5-benzoxazepines are especially intensely studied compounds and various procedures have been worked out for their synthesis.

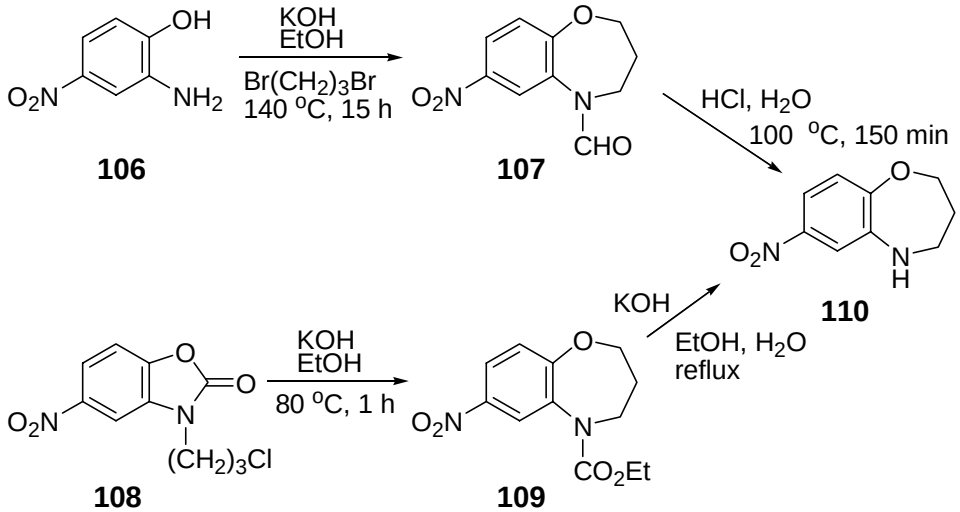
The 2,3,4,5-tetrahydro-1,5-benzoxazepine (**105**) itself has been prepared by the reaction of 2-aminophenol (**104**) with 1,3-dibromopropane in anhydrous dimethylformamide in the presence of sodium hydride (Scheme 39).[88]



104 **105**

Scheme 39

7-Nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**110**) has been synthesized by means of two different multistep procedures. Starting from 2-amino-4-nitrophenol (**106**) first 5-formyl-7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**107**) was obtained which was then converted into the target 1,5-benzoxazepine **110** (Scheme 40).[89] The other method is based on the ring transformation of the 3-(3-chloropropyl)-5-nitro-3*H*-benzoxazol-2-one (**108**) providing 5-ethoxycarbonyl-7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**109**) which was then converted into compound **110** (Scheme 40).[90]

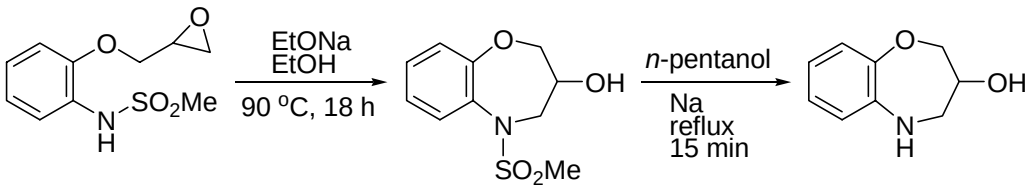


106 **107** **110**

108 **109**

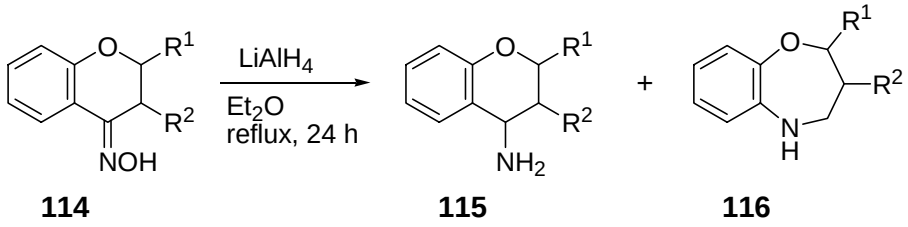
Scheme 40

3-Hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (**113**) was obtained starting from the *N*-mesylated 2-aminophenol derivative **111** which was first cyclized to afford 3-hydroxy-5-mesyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (**112**). Benzoxazepine **112** was demesylated to yield compound **113** (Scheme 41).[91]



Scheme 41

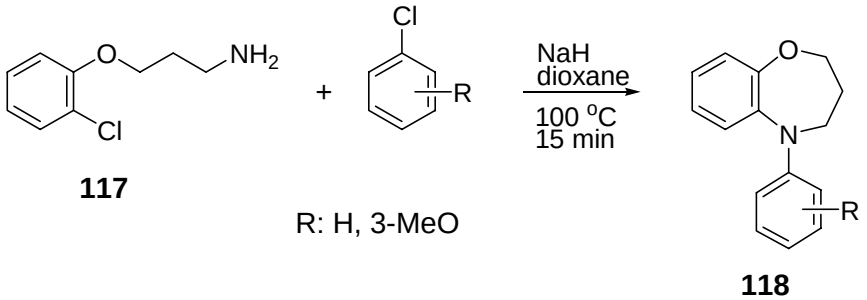
4-Chromanone oximes **114** were reduced by lithium aluminum hydride to prepare 4-aminochromans **115** in several laboratories.[92-95] As by-products, 2,3,4,5-tetrahydro-1,5-benzoxazepines **116** have also been isolated (Scheme 42). However, this reaction cannot be considered as a practical synthesis of such benzoxazepines.



R^1: H, Me, Ar; R^2: H, Ar

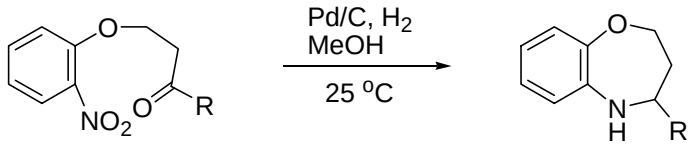
Scheme 42

5-Aryl-2,3,4,5-tetrahydro-1,5-benzoxazepines **118** have been synthesized by the cyclization of amino aryl chlorides **117** *via* an intramolecular arylamination in 1,4-dioxan solution in the presence of sodium hydride (Scheme 43).[96]



Scheme 43

4-Substituted 2,3,4,5-tetrahydro-1,5-benzoxazepines **120** were prepared by the reductive ring closure of nitro carbonyl compounds **119** under 4 atmospheres of hydrogen in the presence of palladium catalyst (Scheme 44).[97]

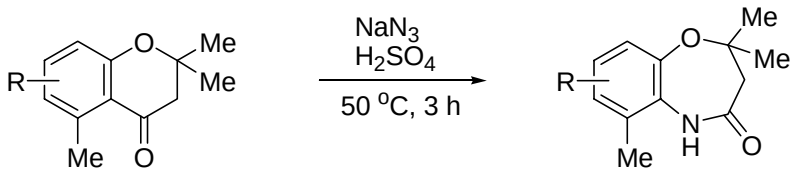


119 **120**

R: H, Me, nBu, Ph

Scheme 44

4-Oxo derivatives of 2,3,4,5-tetrahydro-1,5-benzoxazepines are well known substances and several methods have been developed for their synthesis. A simple procedure is the Schmidt reaction of 2,2,5-trimethyl-4-chromanones **121** to afford 2,2,6-trimethyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **122** (Scheme 45).[47] Formation of these 1,5-benzoxazepine type compounds may be a consequence of the presence of a methyl group at the *peri*-position favouring an aryl migration as a decisive step in the Schmidt reaction.

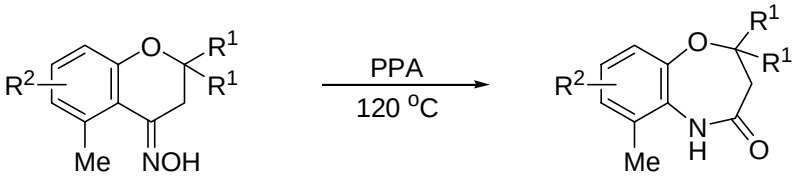


121 **122**

R: H, alkoxy, RSO_2O

Scheme 45

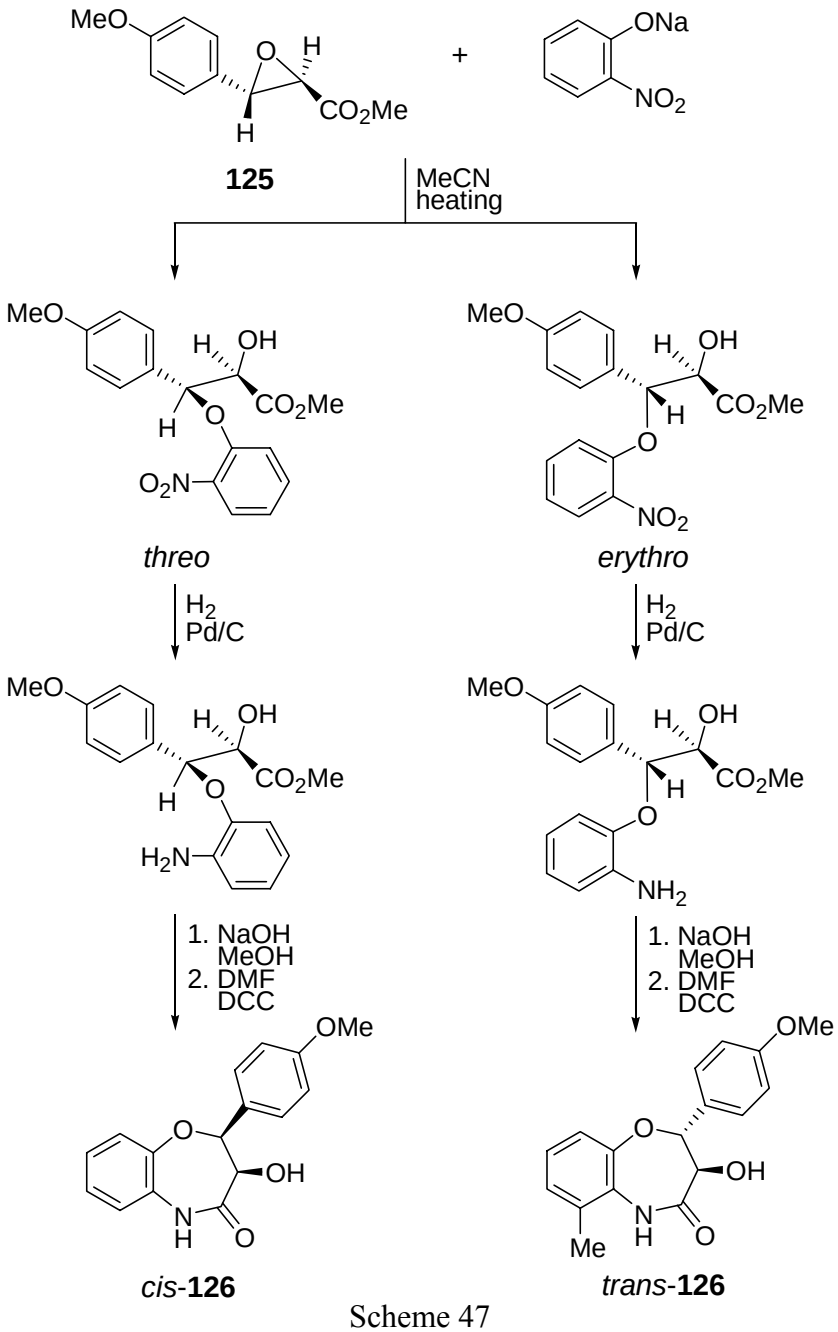
6-Methyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **124** have also been prepared by the Beckmann rearrangement of 5-methyl-4-chromanone oximes **123** (Scheme 46).[52,54] On the basis of these experimental results, it can be concluded that the Schmidt reaction of 4-chromanones and the Beckmann rearrangement of their oximes provide the same 1,5-benzoxazepine isomers.



123 **124**

R^1: H, Me; R^2: H, alkoxy, RSO_2O

Scheme 46

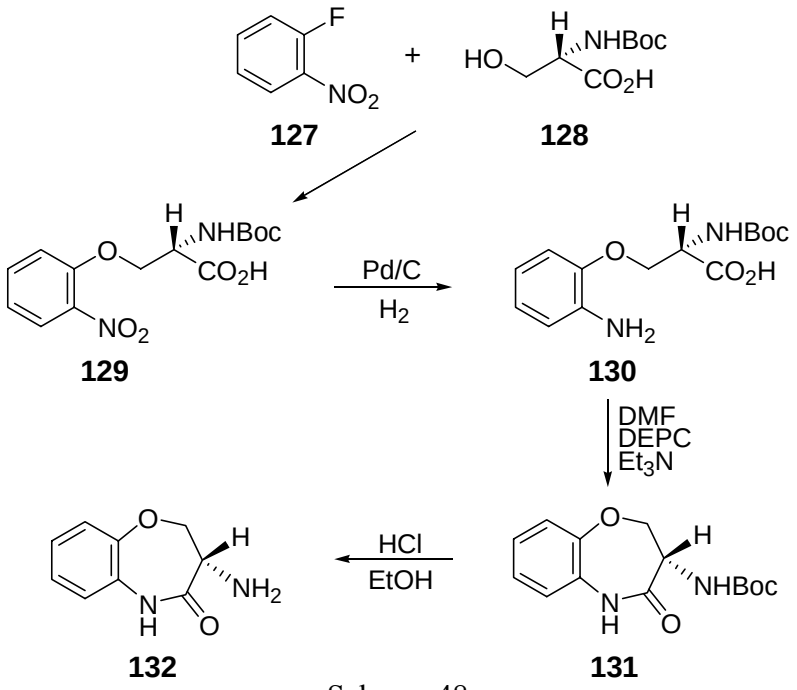


125

cis-**126** *trans*-**126**

Scheme 47

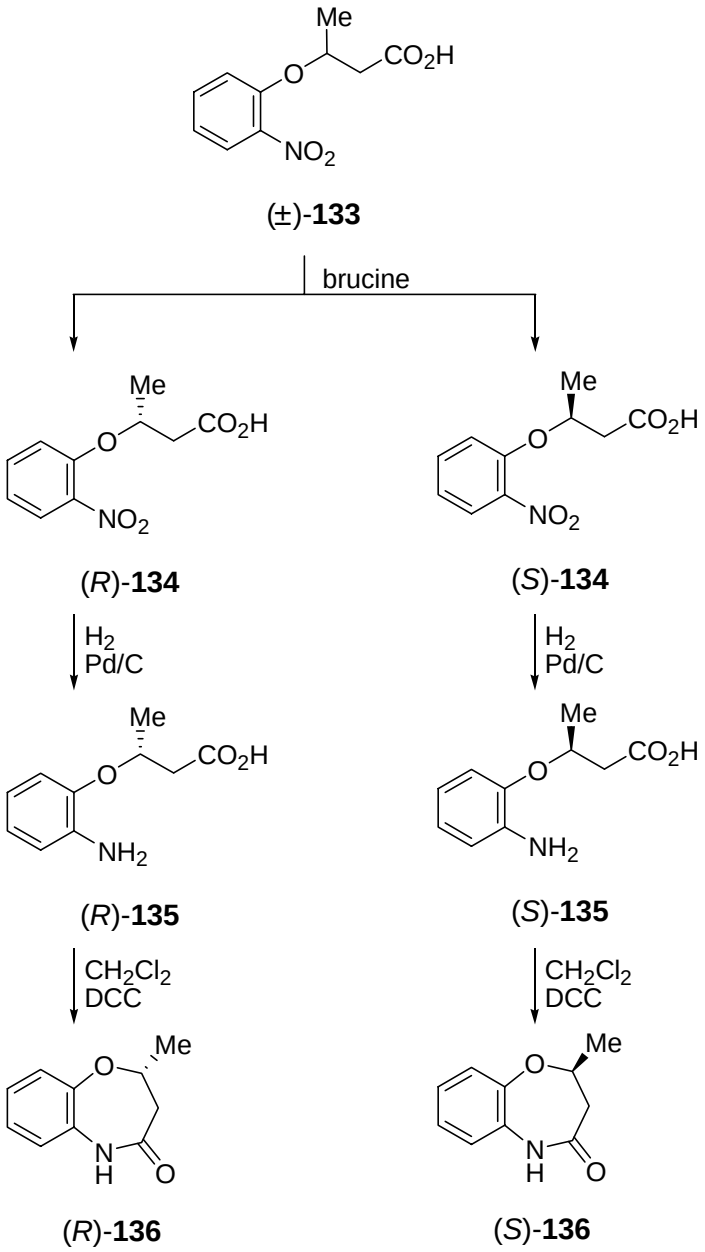
Both *cis*- and *trans*-diastereomers of the 3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (**126**) were prepared starting from *trans*-3-(4-methoxyphenyl)glycidate (**125**) according to a multistep synthetic protocol outlined by Scheme 47.[98]



Scheme 48

Synthesis of optically active 1,5-benzoxazepines has also been described in the literature. (*S*)-3-Amino-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (**132**) was prepared starting by the reaction of 2-fluoronitrobenzene (**127**) with *N*-protected *L*-serine **128**. Nitrocarboxylic acid **129** obtained in this way was reduced to yield aminocarboxylic acid **130**, ring closure of which gave the 1,5-benzoxazepine **131**. Deprotection of the amino group of compound **131** provided the target (*S*)-3-amino-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (**132**) (Scheme 48).[99-101] The origin of the 3*S* absolute configuration of this compound originates from the *L*-serine building block. These optically active 1,5-benzoxazepines have been synthesized as potential angiotensin converting enzyme inhibitors.

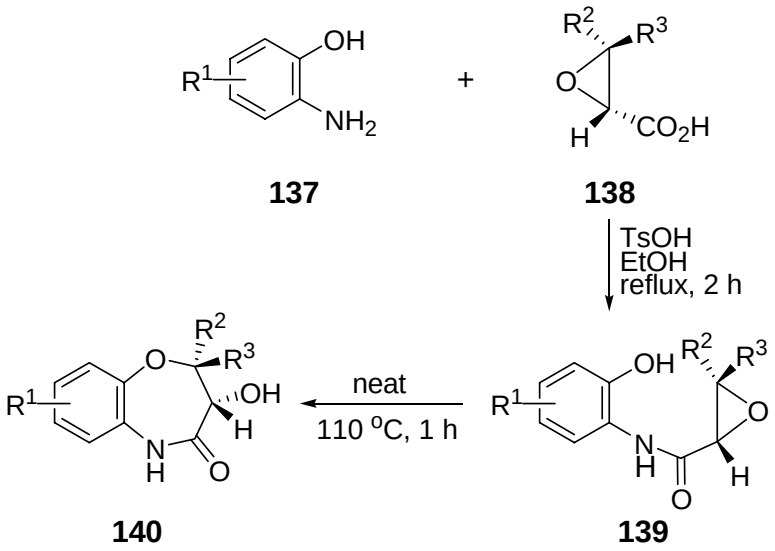
Optically active 2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones have been prepared starting with the optical resolution of the racemic 3-(2-nitrophenoxy)butyric acid (**133**) with brucine[103] or by its enzyme-catalyzed kinetic resolution.[104] Optically active nitrocarboxylic acids **134** obtained in this way were reduced to the appropriate aminocarboxylic acids **135** ring closure of which gave the 2*R* and 2*S* enantiomers of the 2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (**136**) (Scheme 49).[103] Conformation and absolute configuration of these optically active 1,5-benzoxazepines have been determined by NMR spectroscopy[105] and by circular dichroism.[106,107]



Scheme 49

Optically active 3-hydroxy-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **140** have been synthesized by the ring closure of carboxamides **139** obtained by the reaction of optically active oxirane carboxylic acids **138** with 2-aminophenols **137** (Scheme 50).[108]

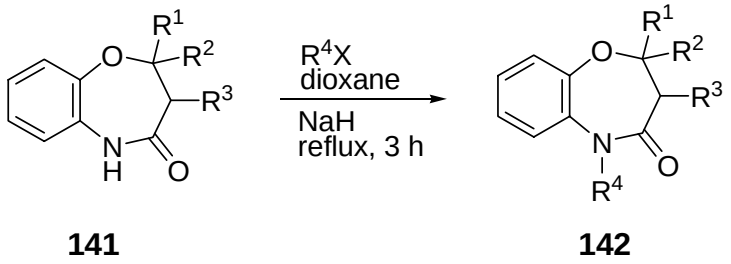
Owing to their bioactivities, 1,5-benzoxazepines are useful substances in the drug research which stimulated the investigation of their chemical transformations. For this reason, some of their derivatizations have been included in this review article.



R^1: H, Me, Cl, NO_2; R^2: H, Me; R^3: H, Pr

Scheme 50

N-Alkylation of the 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones is well documented in the literature.[90,91,98-101,103,109] The appropriate 1,5-benzoxazepine **141** is usually reacted with alkyl halide in anhydrous dimethylformamide in the presence of base to give *N*-alkylated derivatives **142** (Scheme 51). Some *N*-alkyl-1,5-benzoxazepines were found to possess bioactivities, *e.g.* angiotensin converting enzyme inhibitory activity.[99-101]

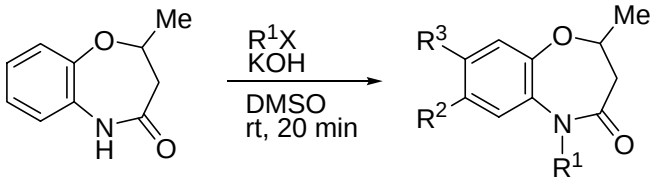


R^1: H, Me; R^2: H, Me; R^3: H, NH_2

R^4: alkyl, aminoalkyl, carboxyalkyl, etc.

Scheme 51

Optically active 2-methyl-2,3-dihydro1,5-benzoxazepin-4(5*H*)-ones **143** were prepared by the chemical transformations of the 2-methyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one enantiomers (*R*)-**136** and (*S*)-**136** (Scheme 52).[103]

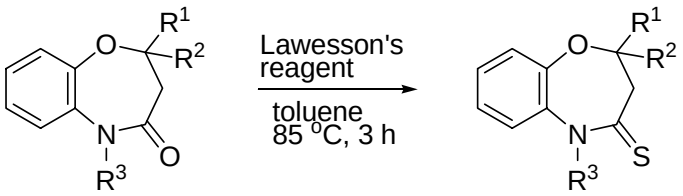


136 **143**

R^1: H, Me, Ac; R^2: H, OH, MeO, Ac, AcO, CO_2H
R^3: H, Cl, Br, NO_2, NH_2, NHAc

Scheme 52

An important chemical transformation is the conversion of the 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **144** into 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-thiones **145**. Compounds **144** were allowed to react with Lawesson's Reagent[72] under anhydrous reaction conditions to yield thioamides **145** (Scheme 53).[47,49,103,110,111]



144 **145**

R^1: H, Me; R^2: H, Me; R^3: H, alkyl

Scheme 53

5. CLOSING REMARKS

In summary, in this review article procedures used for the syntheses of various benzoxazepine isomers are discussed with the help of adequate examples. Most important chemical transformations of the 1,4- and 1,5-benzoxazepines have also been briefly described. Literature data published till the end of 2007 have been included as references to help to find the original synthetic procedures.

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