Chemistry of 1,3-thiazin-4-ones and their derivatives, 1995 – mid-2018

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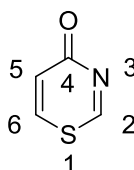*Email: ljs43@psu.edu*

Abstract

This review updates an earlier review published in 1996 by Ryabukhin, Korzhavina, and Suzdalev, which covered the literature through 1994. It deals with the synthesis and reactivity of 1,3-thiazin-4-ones and their derivatives. These include reduced compounds, 2-imino or 2-amino compounds, compounds with fused arenes or heterocycles, bridged compounds, and compounds combining various of these attributes.

Table of Contents

1. Introduction

Compounds with the 1,3-thiazin-4-one ring (Figure 1) have shown bioactivity in many areas, for example muscle relaxant,[1] antitubercular,[2,3] anticancer,[4-6] CXC chemokine receptor 4 (CXCR4) antagonism,[7] antimalarial,[3] antibacterial,[3,8] HIV-RT inhibition,[9] antifungal,[8] antiinflammatory,[10] antioxidant,[11] antihyperglycemic,[12] and cardioprotection.[13]
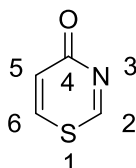
Figure 1

The only comprehensive review of 1,3-thiazin-4-ones and their derivatives was published by Ryabukhin, Korzhavina, and Suzdalev in 1996, covering chemistry through 1994.[14] In this update, the literature from 1995-June 30, 2018 is reviewed. The reader is encouraged to read the original review as well for a comprehensive overview. As in the prior review, 1,3-thiazin-2,4-diones and 1,3-thiazin-2-thione-4-ones are excluded, but 2-imino or their 2-amino tautomers are included. The review is generally organized in the same manner as the earlier review. Synthesis of the ring system is grouped by commonality of the final structure. Reactions of the ring system are grouped by types of reaction.

2. Syntheses

2.1. 1,3-Thiazin-4-ones

2.1.1. 1,3-Thiazin-4-ones. Reaction of (*Z*)-2-cyano-3-sulfanyl-3-(phenylamino)acrylamide **1** with tetracyano-ethylene **2** was found to yield 2,4-dicyano-6-anilino-1,3-thiazin-4-one **3** (Scheme 1).[15] This was suggested to
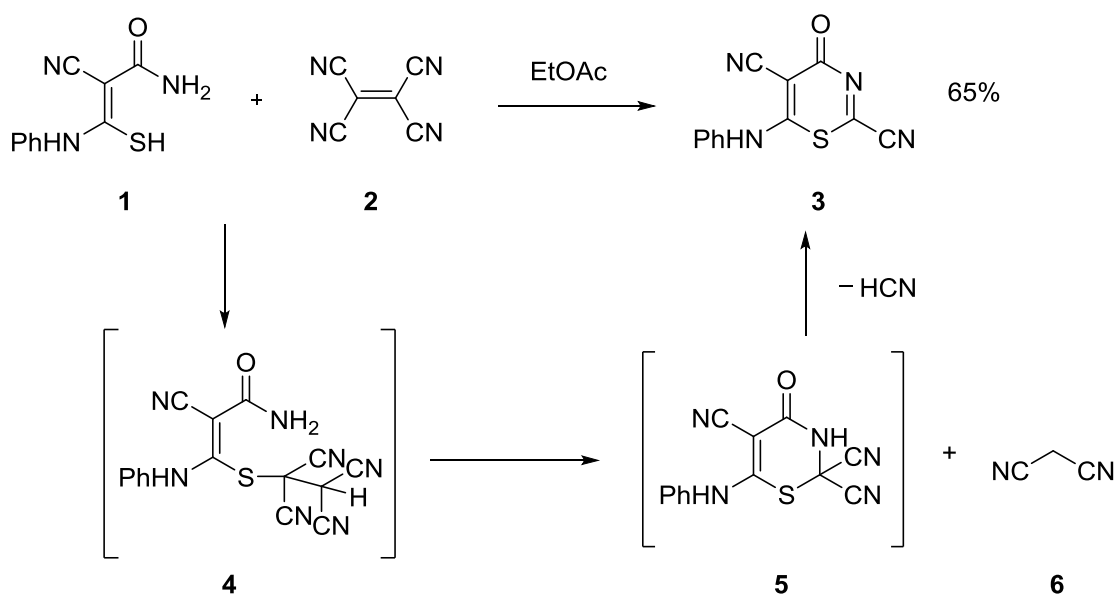
Scheme 1

occur by attack of sulfur on the C=C of **2**, followed by attack of the amide nitrogen on what becomes C2 of the heterocycle. Elimination of HCN then led to **3**.

Thioamides **8** reacted with 3-bromopyruvoyl chloride **7** to give the 5-hydroxy-1,3-thiazin-4-ones **9** in a one-pot, two-step process (Scheme 2).[16] The reaction was shown to proceed through compound **10**, which could be converted into **9** with base.
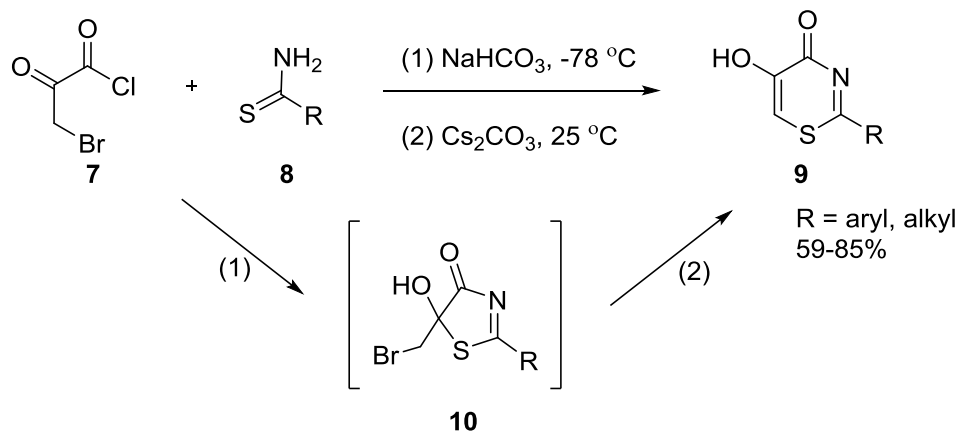
Scheme 2

Oxidation of C2-phenylene bridged *bis*-2,3-dihydro-1,3-thiazin-4-one **11** with nitrobenzene provided the *bis*-1,3-thiazin-4-one **12** (Scheme 3).[17]
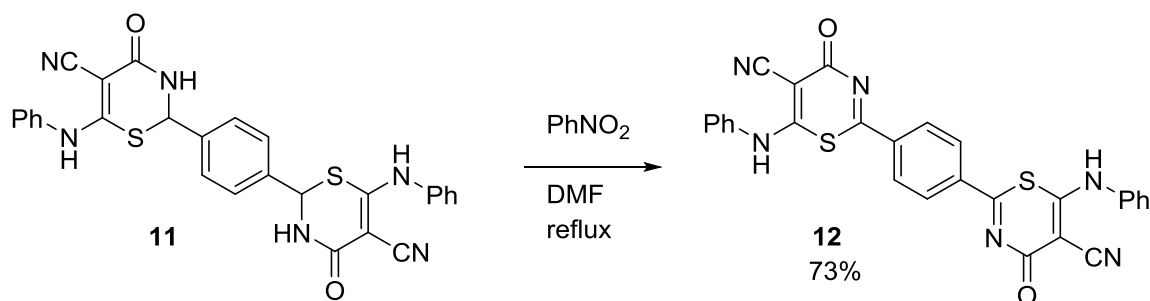
Scheme 3

2.1.2. 2-Imino or 2-amino derivatives of 1,3-thiazin-4-ones. Arylazo cyanoacetate derivatives **13** were shown in two cases to undergo condensation reactions with thiourea **14** to produce the 2,6-diamino-5-azo-1,3-thiazin-4-ones **15** (Scheme 4).[18,19]
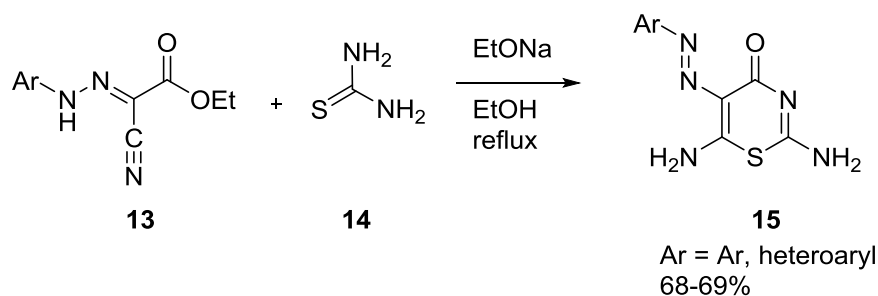
Scheme 4

Similarly, substituted thiosemicarbazide **17** reacted with malonyl dichloride **16** to produce 2-imino-3-amino-6-hydroxy-1,3-thiazin-4-one **18** (Scheme 5). The text of the paper says triethylamine is involved, but the experimental procedure does not.[20]

16   **17**   **18**

Scheme 5

The earlier review mentioned condensation of acetylenic esters with thioureas. It has since been reported that the reaction of acetylenic diesters **19** with dialkylthioureas **20** can be run with water as the solvent and triphenylphosphine as catalyst is a simple procedure (Scheme 6).[21] There was no reaction without the catalyst.

19   **20**   **21**
R^1 = Me, Et
R^2 = Me, Et, Ph
83-92%

Scheme 6

The 2-imino-1,3-thiazin-4-one **24** was the result of a dehydrogenation that occurred when the 2-imino-2,3-dihydro-1,3-thiazin-4-ones **22** (see Schemes 36 and 38 for preparation) were heated to 160 °C with phenacyl bromides **23** (Scheme 7).[22] Similar reactions can be found in Schemes 18 and 87.

22   **24**
Ar^1 = Ph, *p*-FC$_6$H$_4$
Ar^2 = Ph, *p*-ClC$_6$H$_4$
29-33%

Scheme 7

2.2. 1,3-Benzothiazin-4-ones

2.2.1. 1,3-Benzothiazin-4-ones. 2-Fluorobenzoyl chlorides **25** were converted to 2-fluoro-1-benzoyl isothiocyanates **26** by treatment with ammonium thiocyanate in a solvent at 40 °C. NH$_4$Cl was filtered off and the solution of **26** was combined with nucleophilic methylenes **27** to produce addition products **28**. Treatment with triethylamine in refluxing toluene induced cyclization to 2-vinyl 1,3-benzothiazin-4-ones **29** (Scheme 8).[23] The reaction appears to proceed by addition of the *C*-nucleophile to the isothiocyanate, and then intramolecular cyclization *via* nucleophilic aromatic substitution. When (pyridine-2-yl)acetonitrile **30** wa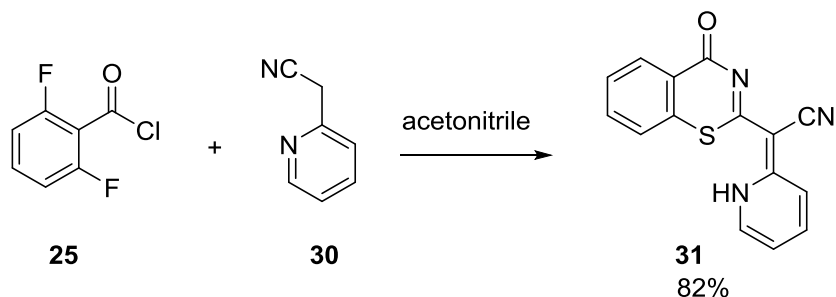s used in place of **27**, both steps took place in acetonitrile at room temperature (Scheme 9).[23] Reactions of **27** with polyfluorinated analogs of **26** also in some cases needed triethylamine for the cyclization and in some cases didn't.[24] Some other examples using *N*-nucleophiles are discussed in Section 2.2.2.
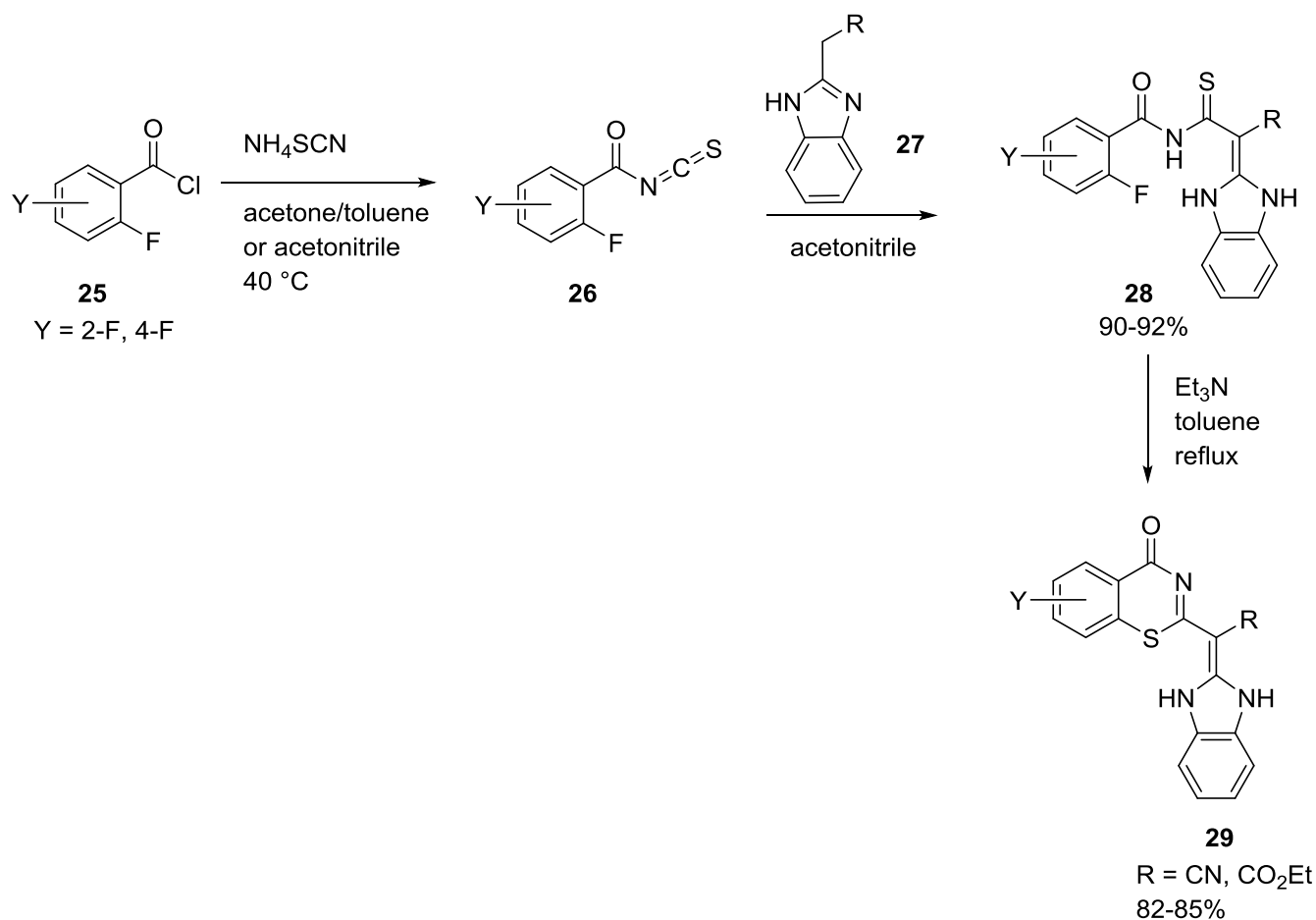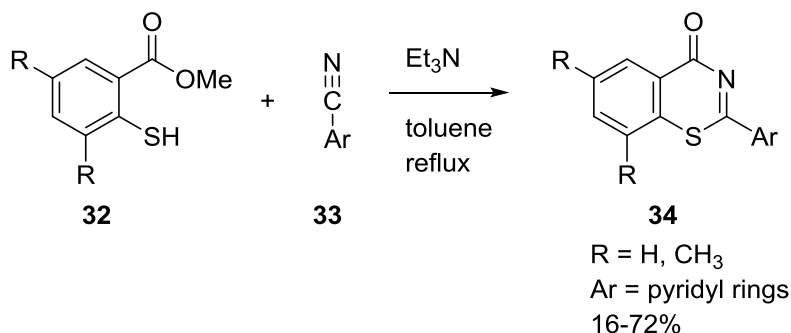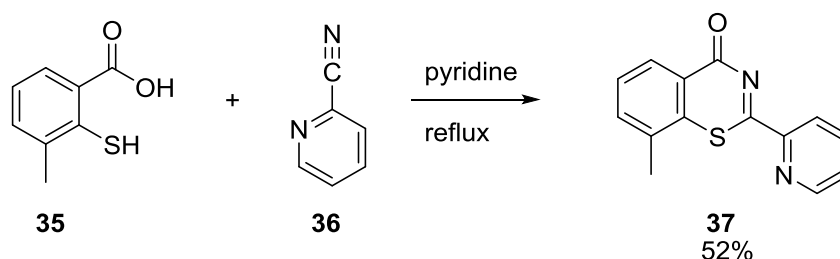

Scheme 8

Scheme 9

Methyl 2-sulfanylbenzoates **32**, aryl nitriles **33** and triethylamine were heated to reflux in toluene to give products **34** (Scheme 10).[13] This is a variant on the commonly used reaction of a 2-sulfanylbenzoic acid **35**, one of which was also used, in pyridine (Scheme 11).

R = H, CH$_3$
Ar = pyridyl rings
16-72%

Scheme 10

37
52%

Scheme 11

2.2.2. 2-Imino or 2-amino derivatives of 1,3-benzothiazin-4-ones. 2-Halo-1-isothiocyanates **38** condensed with amines **39** produced 2-amino-1,3-benzothiazin-4-ones **40** *via* nucleophilic aromatic substitution (Scheme 12). Examples where the halogen is fluorine[25-28] or chlorine[29] have been reported in recent years. In the example given (X = Cl) in the earlier review, the ring closure was performed using lithium hydride, but in the cases reported since it was done either with triethylamine or with no base at all.[25-27,29] One example where X = F used sodium hydride in THF and DMF at 110 °C.[28] The amine **39** may be a hydrazine,[25] an amino-heterocycle,[26] an aryl amine,[28] or a cyclic amine.[27,29]

38
X= F, Cl
Y = H, 3,4,5-F

41
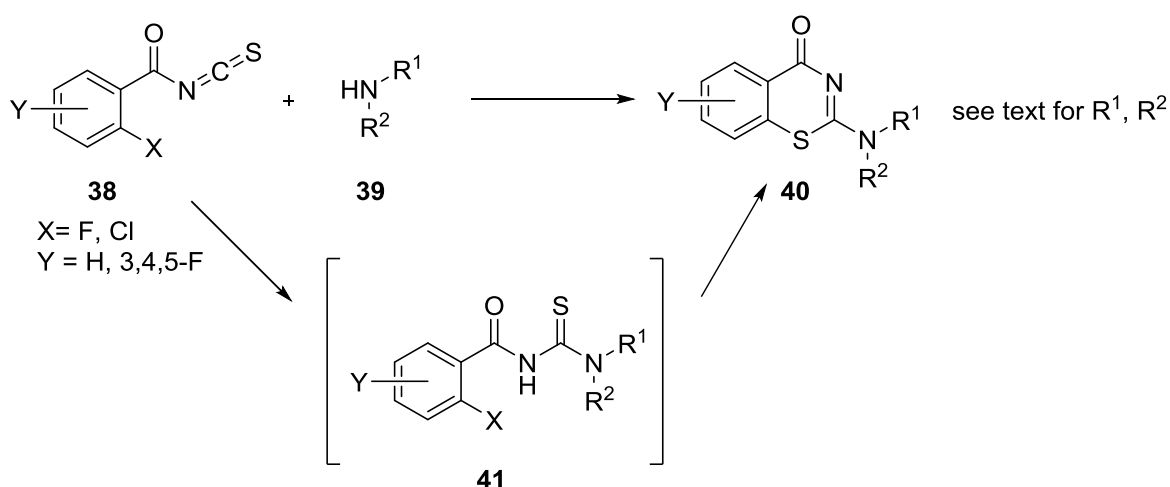
Scheme 12

It recently was demonstrated that by use of *t*-butyl sulfoxid**e** as a sulfenic acid equivalent, 2-(*t*-butylsulfinyl)benzamide **42** reacted with isocyanobenzene **43** to produce the 2-anilino-compound **44** (Scheme 13).[30] The pathway of the reaction began with thermolysis of **42** to give the sulfenic acid **45**. Condensation of **45** with isocyanobenzene **43** led to carbocation **46** which was then attacked by the amide nitrogen to close the ring.
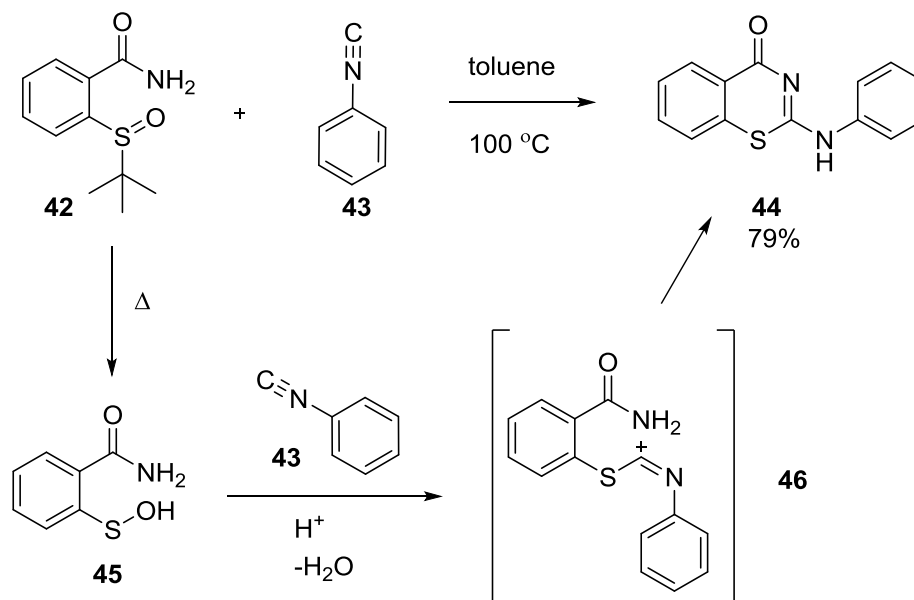
Scheme 13

2-Sulfanylbenzoic acid **47** reacted with cyanamides **48** in refluxing dioxane to yield the 1,3-benzothiazin-4-ones **49** (Scheme 14). In this case, attack of the thiol group of **47** on the nitriles **48** was presumed to give intermediates **50**, which cyclized to give **49**.[3]
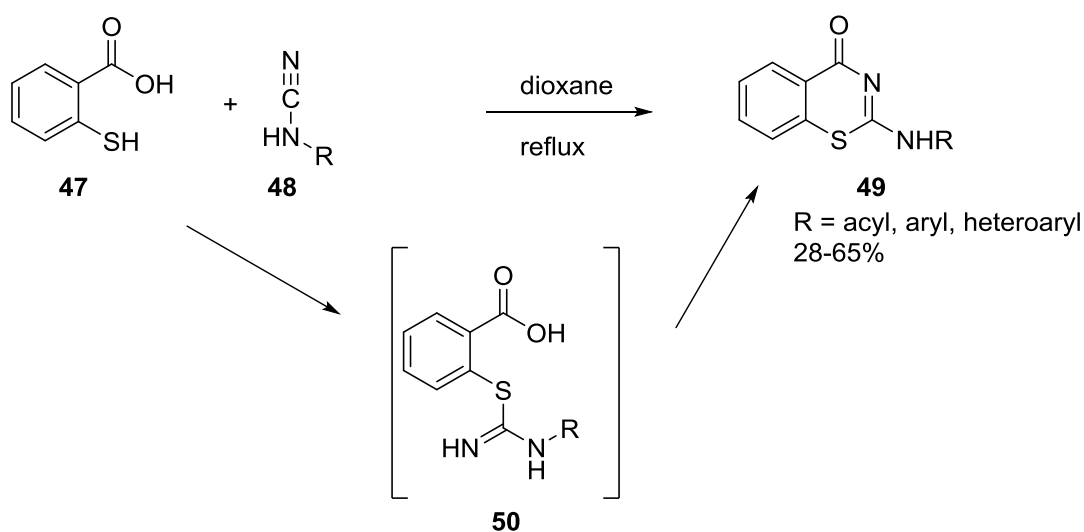
Scheme 14

Treatment of 2,3,4,5-tetrafluoro-1-benzoylisothiocyanate **51** with imidazolidine-2-thione **52** produced compound **53**, which with triethylamine gave the cyclized 1,3-benzothiazin-4-one **54** (Scheme 15).[32]
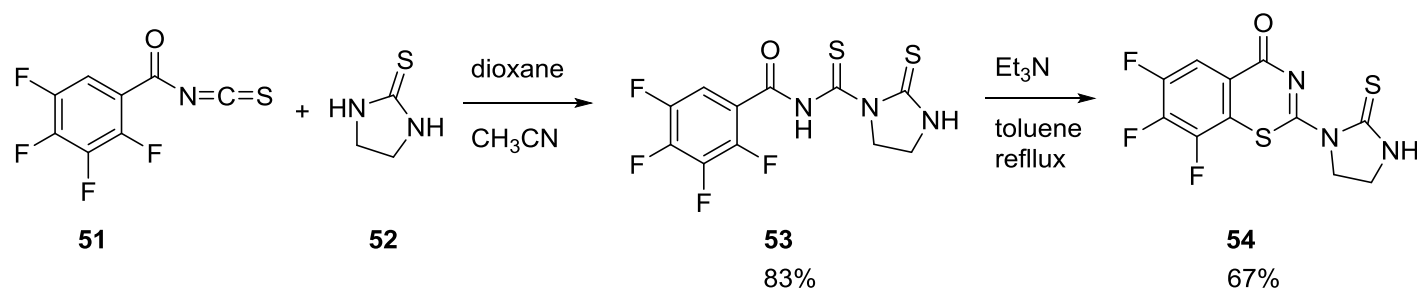
Scheme 15

Nucleophilic substitution was used to convert 2-methylthio-1,3-benzothiazin-4-ones **55** to 2-cycloamino compounds **57** (Scheme 16).
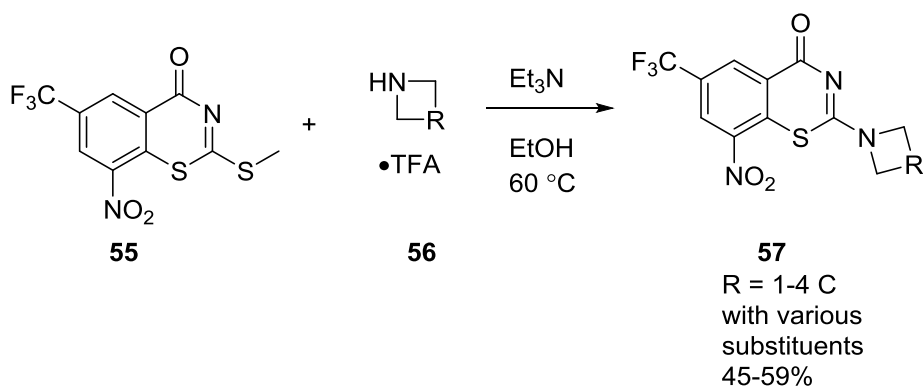
Scheme 16

2.3. Reduced 1,3-thiazin-4-ones
2.3.1. 2,3-Dihydro-1,3-thiazin-4-ones with an exocyclic C=C.
Reaction of **1** with 2-dicyanomethyleneindane-1,3-dione **58** gave product **59** with an exocyclic C=C at C2 (Scheme 17).[15] The reaction path was proposed to be similar to that in Scheme 1.
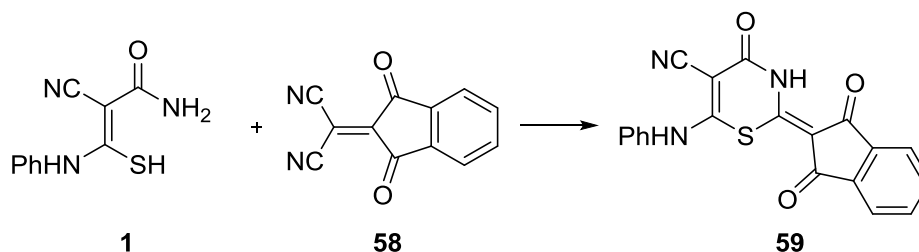
Scheme 17

The 2-methylidene-2,3-dihydro-1,3-thiazin-4-one **62** was the result of a dehydrogenation reaction that occurred when the 2-methylidene-2,3,5,6-tetrahydro-1,3-thiazin-4-one **60** (see Scheme 51 for synthesis) was heated to 150 °C with phenacyl bromide **61** (Scheme 18).[33] Similar reactions are shown in Schemes 7 and 87.

Scheme 18

2.3.2. 2-Imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones with an exocyclic C=C. The 2-bromoethyl-alkenoates **63** were found to react with thiourea **14** in aqueous acetone to give the isothiouronium intermediate **64**. After a wash with dichloromethane, the aqueous layer was treated with sodium bicarbonate to give the 1,3-thiazin-4-one **65**, with an exocyclic C=C at C5, and an amine at C2 (Scheme 19). A proposed mechanism involved nucleophilic attack of the sulfur to displace the bromine, giving the isothiouronium bromides **64**. Treatment with base removed HBr and cyclization occurred with loss of methanol.[34]
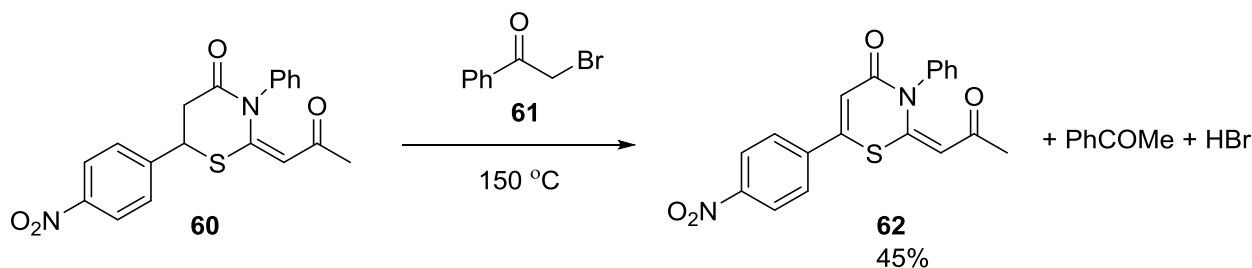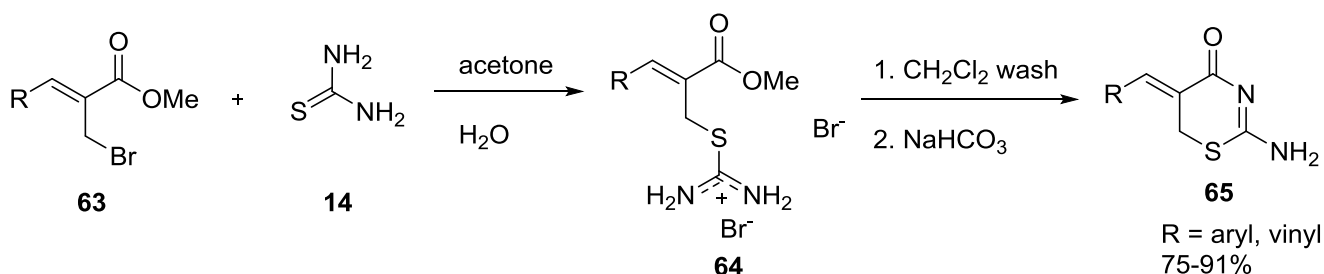

Scheme 19

2.3.3. 2,3-Dihydro-1,3-thiazin-4-ones. In the earlier review, the only syntheses presented of this group were a few ring-expansion reactions. Since then, some other types of syntheses have been developed.

In one method, aryl isothiocyanates **66** were reacted with cyanoacetamide **67** under basic conditions to give the isolated products **68**. These intermediates were then reacted with an aldehyde **69** and cyclized with *p*-toluenesulfonic acid (TsOH) catalyst at room temperature to give 5-cyano-6-arylamino-2,3-dihydro-1,3-thiazin-4-ones **70** (Scheme 20).[35] This has also been done in one pot using aldehydes or acetone. The reaction was also performed with NaOH in DMF at room temperature, then acetic acid and acetone were added and the mixture was heated by microwave irradiation to 80 °C (Ar = Ph, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$; R = alkyl, aryl, heteroaryl; 84-93%).[36]
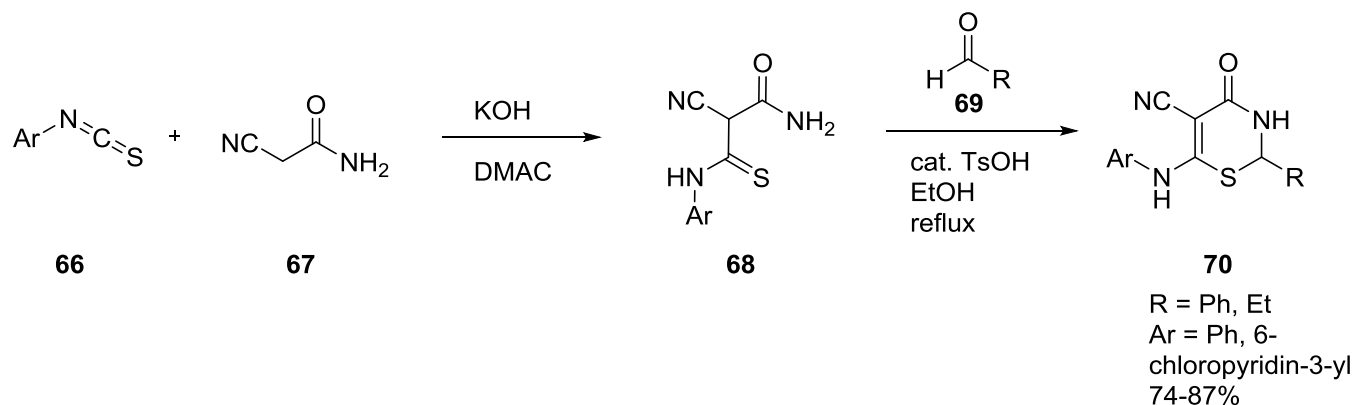
Scheme 20

In another method, 3-alkyl(aryl)amino-2-cyano-3-sulfanylacrylamides **1** reacted with aldehydes and ketones **71**, with catalytic TsOH as above, to produce compounds **72** (Scheme 21).[17,37-41]
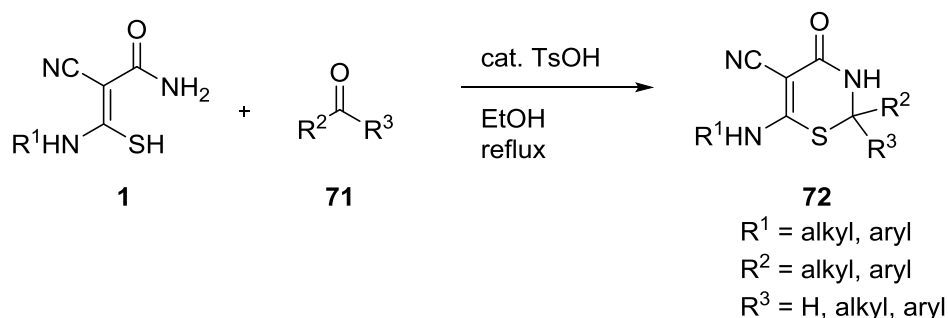
Scheme 21

The catalyst does not seem to be necessary. A similar reaction has also been reported, in which compounds **1** were simply dissolved in a ketone solvent or anisaldehyde and then allowed to crystallize products **72**.[42] Another version involved a single example of an aryl aldehyde and ethanol at reflux, without TsOH.[43]

A variety of 2-spiro compounds **75** were synthesized in a two-step, one-pot procedure beginning with reaction of isothiocyanates **73** with cyanoacetamide **67** in DMF-catalyzed sodium hydroxide to produce **1**. Addition of cyclic ketones **74** and acetic acid and then microwave irradiation gave the products **75** (Scheme 22).[44]
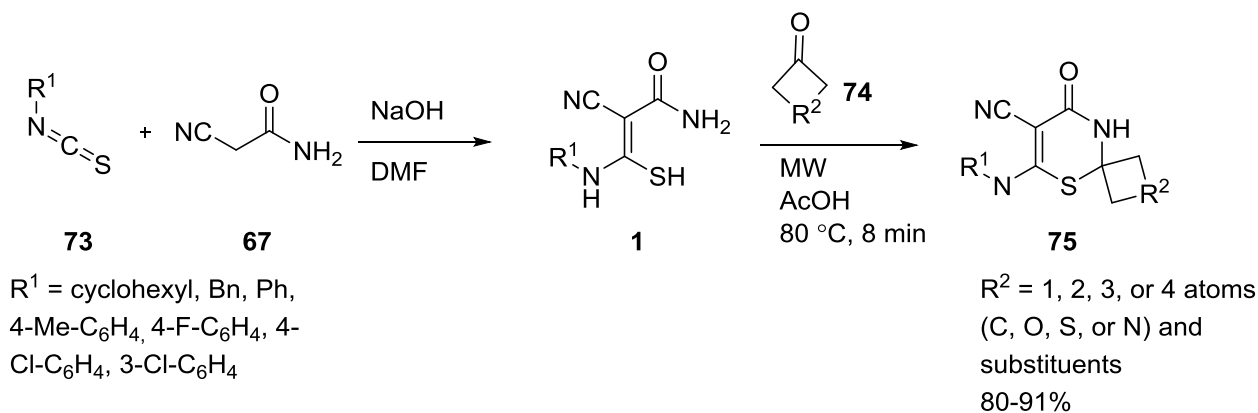
Scheme 22

2.3.4. 5,6-Dihydro-1,3-thiazin-4-ones. In one recent method, malononitrile **6** was reacted with dimedone **76** to produce derivative **78,** which was refluxed in acetic acid with thioacetamide **79** in the presence of sodium acetate to form the 2-methyl-6-spiro-5,6-dihydro-1,3-thiazin-4-one compound **80** (Scheme 23).[45]
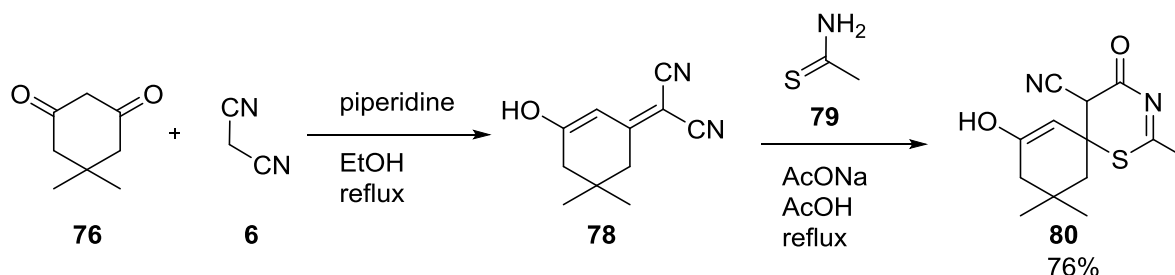
Scheme 23

In a method involving an isothiocyanate, treatment of the crude unstable compound **81** with amines **82** produced thioureas **83**. Intramolecular cyclization was accomplished with boron trifluoride to produce 5,6-dihydro-1,3-thiazin-4-ones **84** (Scheme 24).[46]

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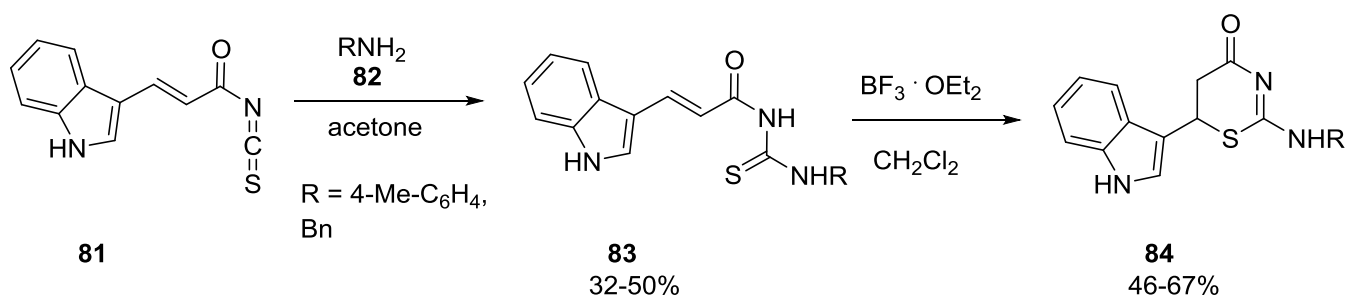
Scheme 24

2.3.5. 2-Imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones. Many of the approaches to these compounds involve thioureas.

Sulfonylthioureas **86** reacted with ethyl 3-bromopropionate **85** in the presence of sodium acetate in refluxing ethanol[47-56] or acetic acid[56,57] to give the products **87** (Scheme 25). In two cases ethanol alone was used.[58,59]
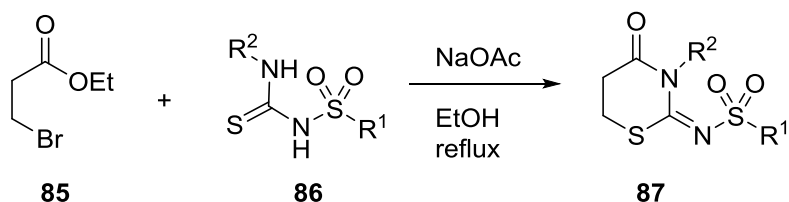
Scheme 25

This also worked when there was a carbonyl group in place of the sulfone (Scheme 26).[60]
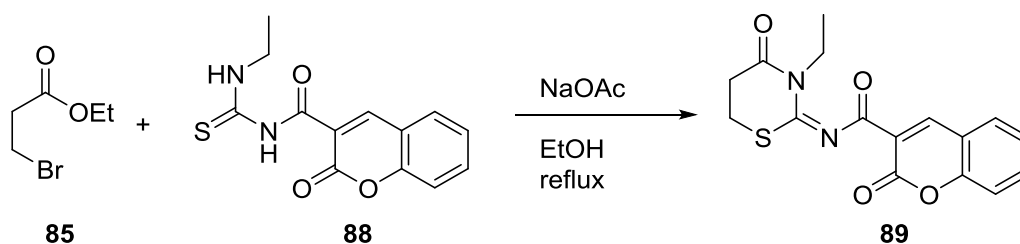
Scheme 26

Reaction of thioureas **19** with ethyl 3-bromopropionate **85** was done just by refluxing in dioxane to give compounds **90** (Scheme 27).[61-63] Refluxing ethanol has also been used.[64]

R^1 = alkyl, aryl, *N*-imino
R^2 = alkyl, aryl
70-92%
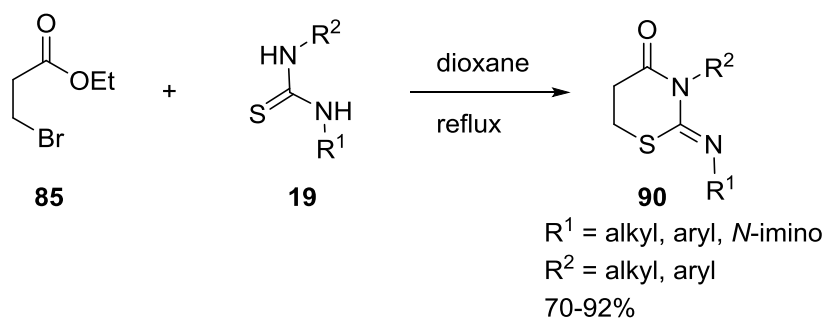
Scheme 27

Reaction of 3-chloropropanoic acid **91** with thiosemicarbazones **92** under typical conditions (NaOAc, AcOH, Ac$_2$O) gave yields of products **94** of 44-48%, whereas use of the ionic liquid *N*-methylpyridinium *p*-toluenesulfonate **93** gave 74-75% yields (Scheme 28).[65] Dicyclohexylcarbodiimide (DCC) in THF at 0 °C has also been used in this type of reaction (55%).[66]
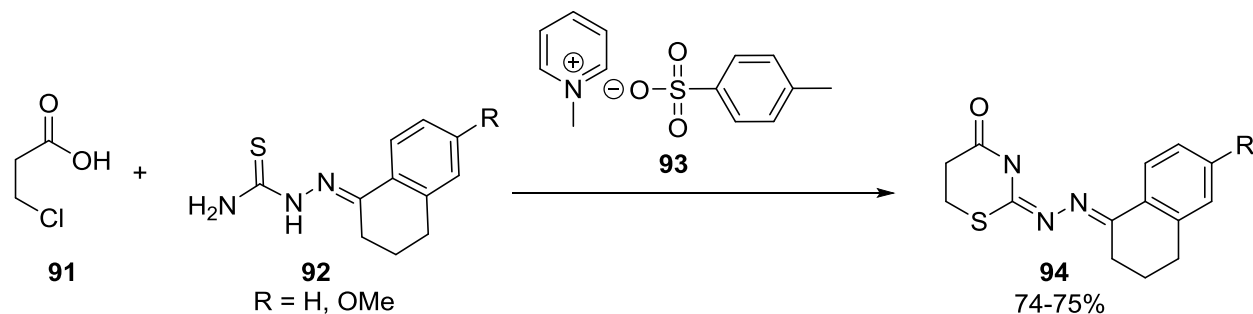
Scheme 28

3-Chloropropanoyl chloride **95** and potassium thiocyanate were refluxed in acetone and then 2,4-dimethylaniline **96** was added at room temperature to produce 2-imino-5,6-dihydro-1,3-thiazin-4-one **97** (Scheme 29).[67] Use of 3-bromopropanoyl was discussed in the earlier review.
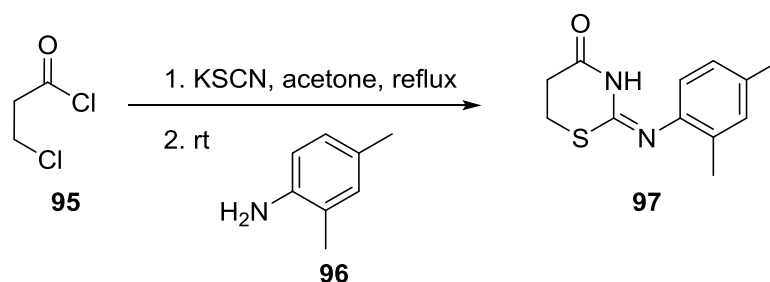
Scheme 29

Previously it had been reported that the known thermal reaction of methacroyl isothiocyanate **98** with isonicotinylhydrazide **99** led to the 2-hydrazide-1,4-diacyl-thiosemicarbazide **100,** which when heated to 70 °C in 2-propanol gave compound **103** (65% from **100**).[68] It was then found that addition of a cyclic secondary amine base **101** promoted the intramolecular (conjugate-addition) cyclization of **100**, making the reaction run faster, at lower temperature (30 °C) and in higher yield (82%) (Scheme 30). It was proposed by the authors that the base mediates formation of the thiol tautomeric form **102** of **100** to allow its cyclization.[69]

Methacroyl isothiocyanate **98** was prepared *in situ* by reaction of KSCN with methacroyl chloride**,** and then treatment with morpholin-4-amine or adamantane-1-amine generated the thiourea **100**, which then cyclized to the product as in Scheme 30.[10]

Under the same conditions as the reaction shown in Scheme 23, replacement of thioacetamide **79** with thioureas **104** gave the 2-amino-5-cyano-6-spiro-5,6-dihydro-1,3-thiazin-4-ones **105** (Scheme 31).[45]
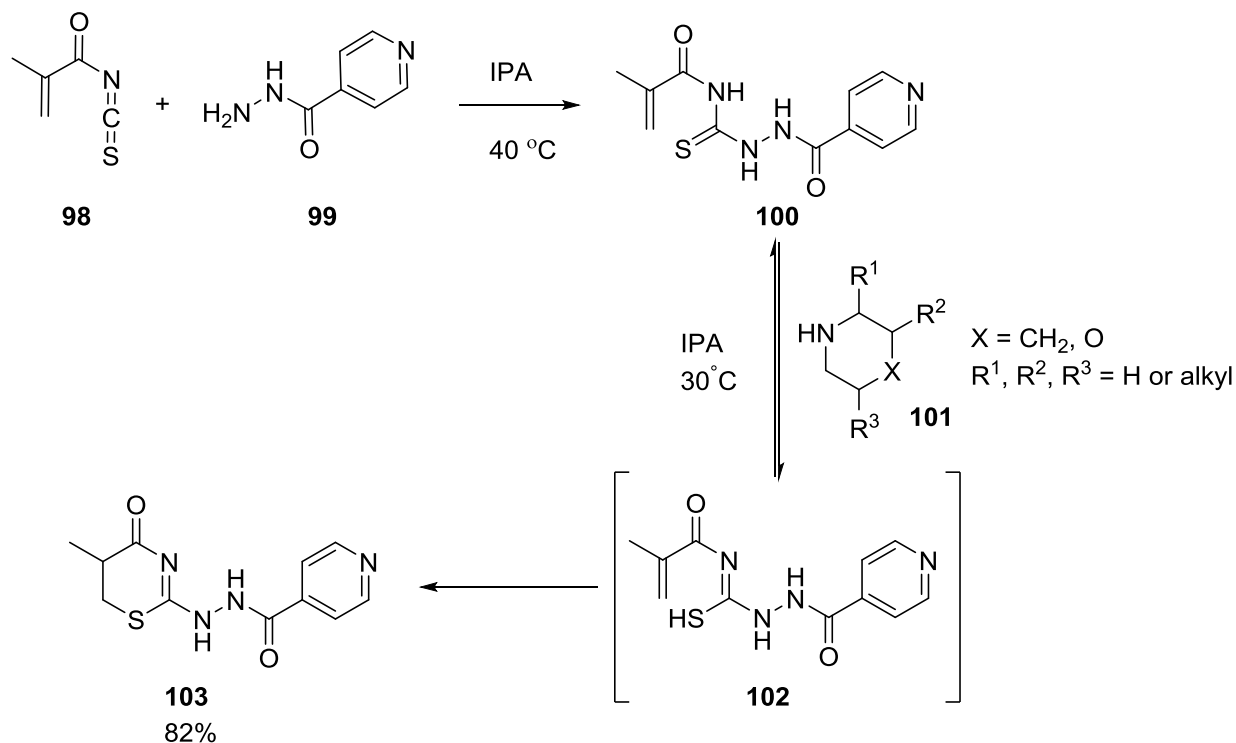
Scheme 30
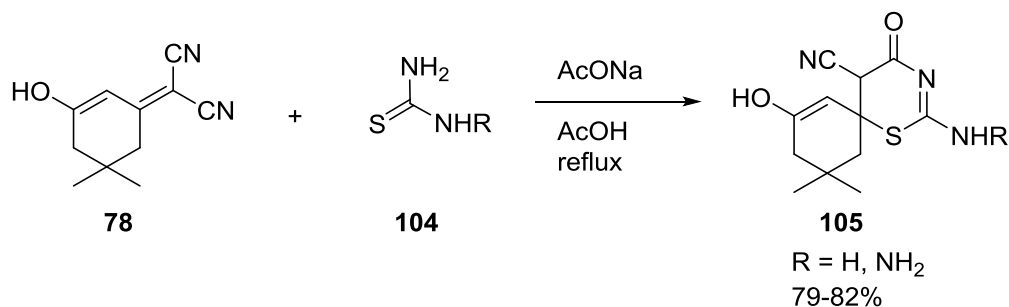
Scheme 31

A number of preparations involve conjugate addition of the thiourea derivative. A three-component reaction of a primary alkyl amine **82**, phenylisothiocyanate **107,** and 2-propenoyl chloride **106** in the presence of triethylamine produced the 2-amino compounds **108** (Scheme 32). The thiourea derivative was presumably formed *in situ* from the amine and the isothiocyanate. The reaction only gave the product in which the ring nitrogen bears the phenyl substituent.[70]
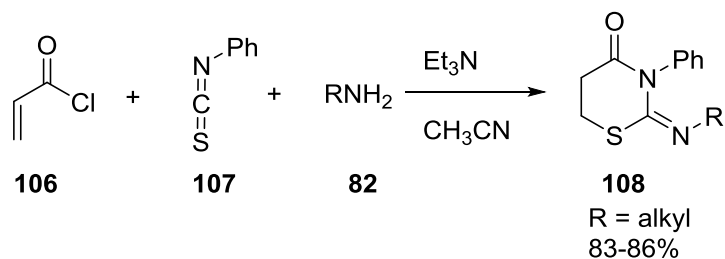
Scheme 32

A three-component reaction of amines **109**, isocyanates **73**, and itaconic anhydride **110** gave 5-acetic acid products **111** (Scheme 33). A possible pathway involved initial attack of the amines **109** on the isothiocyanates **73** to give substituted thioureas **112**, followed by attack of the sulfur on the exocyclic double bond in a conjugate addition to open the ring, then cyclization by the nitrogen attacking the ketene intermediates **113**.[71]
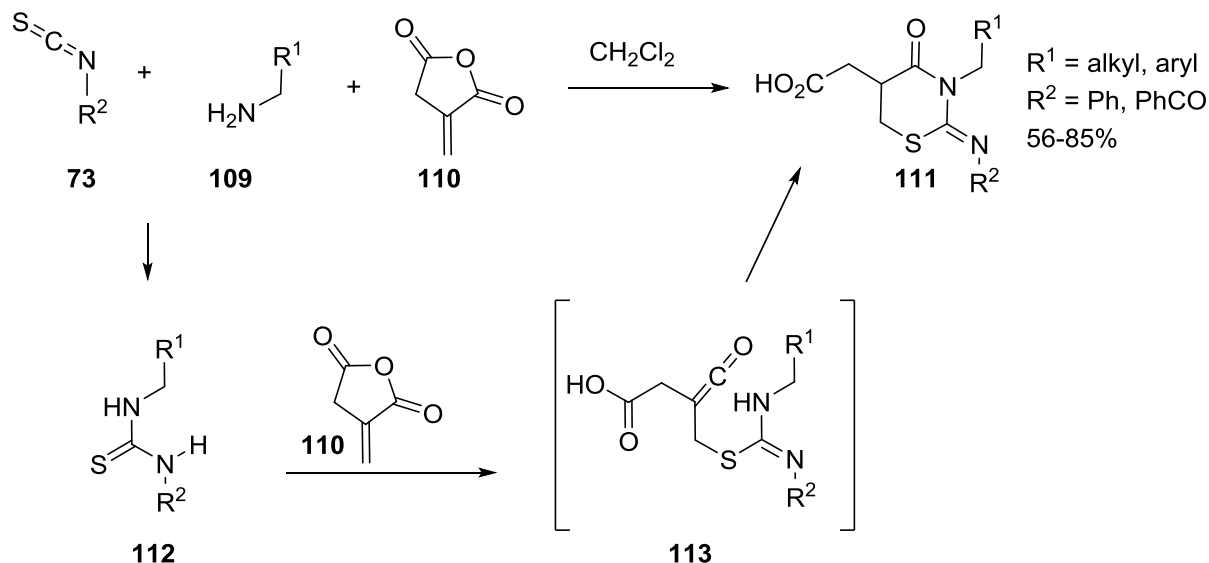
Scheme 33

A one-pot reaction, in the presence of ionic liquid catalyst [Bmim]Br **117**, of 2-phenyl-1,3-oxazol-5-one **114** or 2-methyl-2-phenyl-1,3-oxathiolan-5-one **115** with aldehydes **116**, followed by addition of thioureas **104** gave the 2,5-diamino-6-aryl-5,6-dihydro-1,3-thiazin-4-ones **120** or 2-amino-6-aryl-5-mercapto-5,6-dihydro-1,3-thiazin-4-ones **121** with high diastereoselectivity (Scheme 34). The proposed mechanism was a first step of condensation of the aldehydes **116** with the esters **114** or **115,** then conjugate addition of the sulfur of thiol tautomeric form of thioureas **104** to give intermediate **122** or **123**, and then an intramolecular cyclization to give the products **120** or **121**. The ionic liquid **117** was said to hydrogen bond to the carbonyl oxygen, making the carbon more electrophilic (not shown in Scheme).[72]

Cyclization *via* intramolecular conjugate addition has also been reported. Treatment of thiourea derivative **125** with sodium ethoxide in ethanol at room temperature led to the product **126**, as the kinetic product resulting from attack of the thiolate anion on the alkene.[73,74] When the reaction was run at reflux, the thermodynamic product **124** resulting from attack by nitrogen was obtained (Scheme 35).[74] The room temperature reaction has been shown to work in other examples as well.[73,75-77]
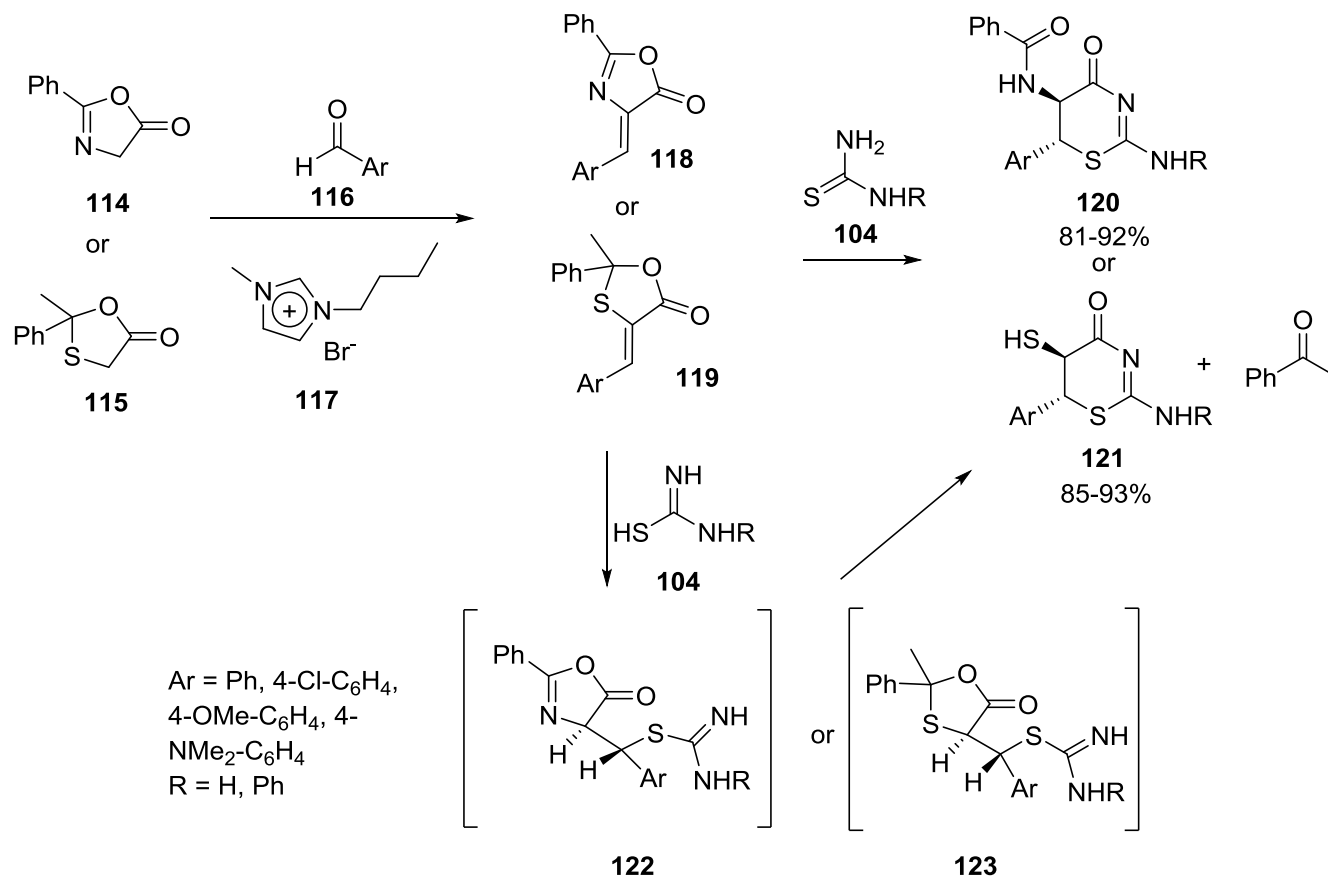
Scheme 34
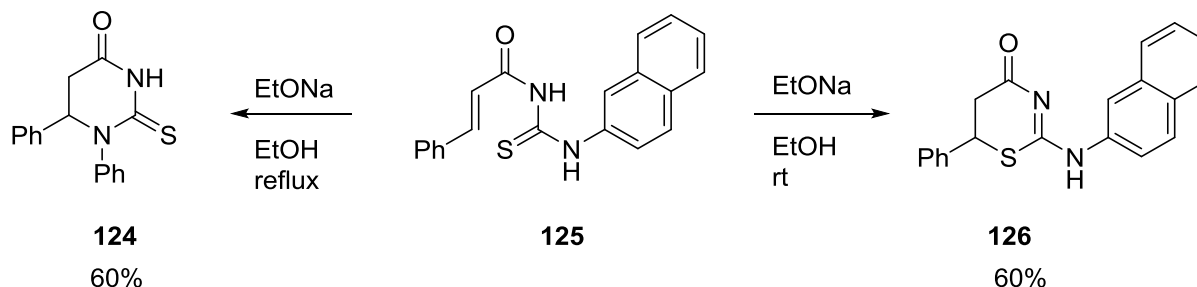
Scheme 35

The same type of reaction was shown to be catalyzed by HCl in acetone (Scheme 36). The initial product was the HCl salt. Treatment with sodium bicarbonate or potassium bicarbonate removed the acid to give **128**.[22,78] Boron trifluoride also has been shown to catalyze this type of cyclization.[79]

Ar = Ph, 4-F-C$_6$H$_4$, 4-OMe-C$_6$H$_4$,
2-thienyl
R^1 = H, Me
R^2 = H, Me
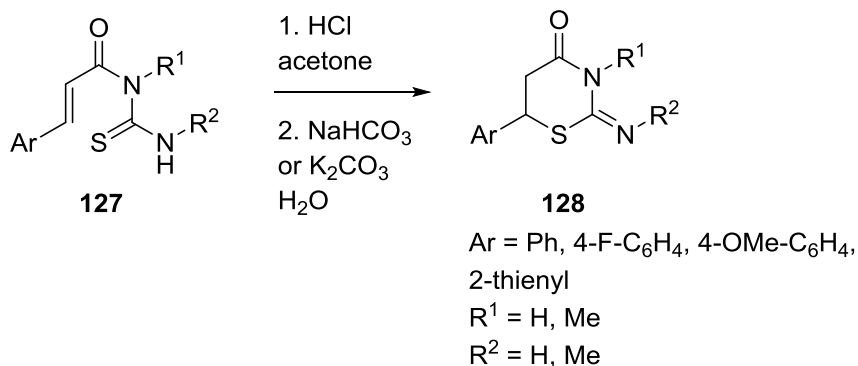
Scheme 36

In one particular case, this type of cyclization took place in refluxing acetone alone (Scheme 37).[80]
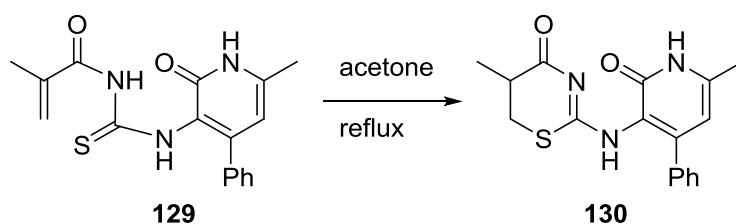
Scheme 37

A one-pot reaction was done in which thioureas **132** were reacted with 3-aryl-2-propenoyl chlorides **131** in acetone to give products **133** (Scheme 38).[22] For R = H, the product was the HCl salt of **133**. It was presumed that the *N*-acylation product was formed first, followed by cyclization as in the examples above.

131
Ar = Ph, 4-OMe-C$_6$H$_4$,
4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$,
3-NO$_2$-C$_6$H$_4$, 2-thienyl

132

133
R = H, Ph
65-74%
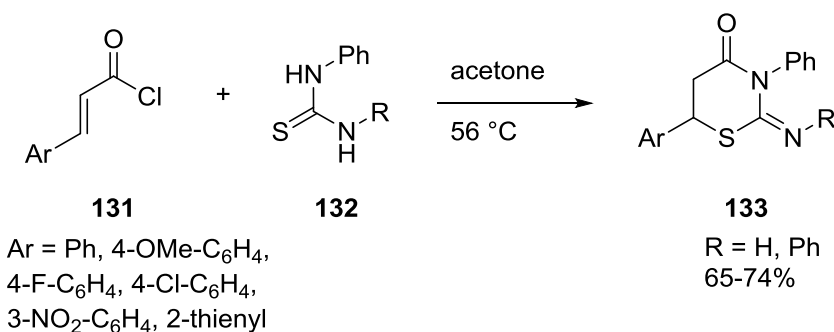
Scheme 38

The bioactive compound **136** was synthesized by heating an acetic acid solution of *N,N'*-dimethylthiourea **135** with *N*-(4-chlorophenyl)maleimide **134** (Scheme 39).[81]
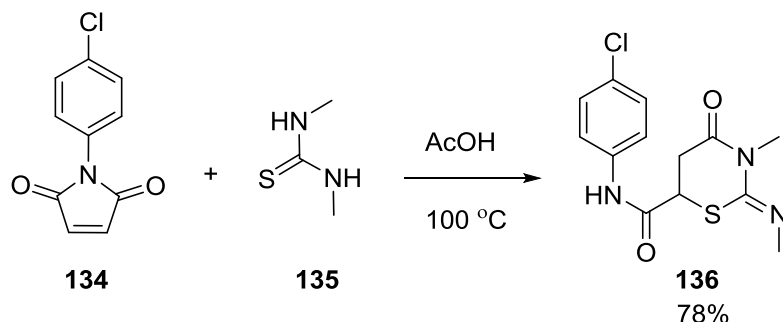
Scheme 39

Another novel reaction involving a ring-opening combined thiourea derivatives **138**, 2,3-diphenyl-cyclopropenone **137**, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give **139** (Scheme 40)**.** The mechanism was proposed to begin with conjugate addition of the sulfur to the cyclopropenone to give intermediate **140**. The strained ring then opened, producing intermediate **141**, and then intramolecular attack of nitrogen on the ketene gave compound **142** which then was oxidized by DDQ to product **139**. Compound **142** was isolated in a separate experiment and shown to undergo DDQ oxidation to provide **139**.[82]
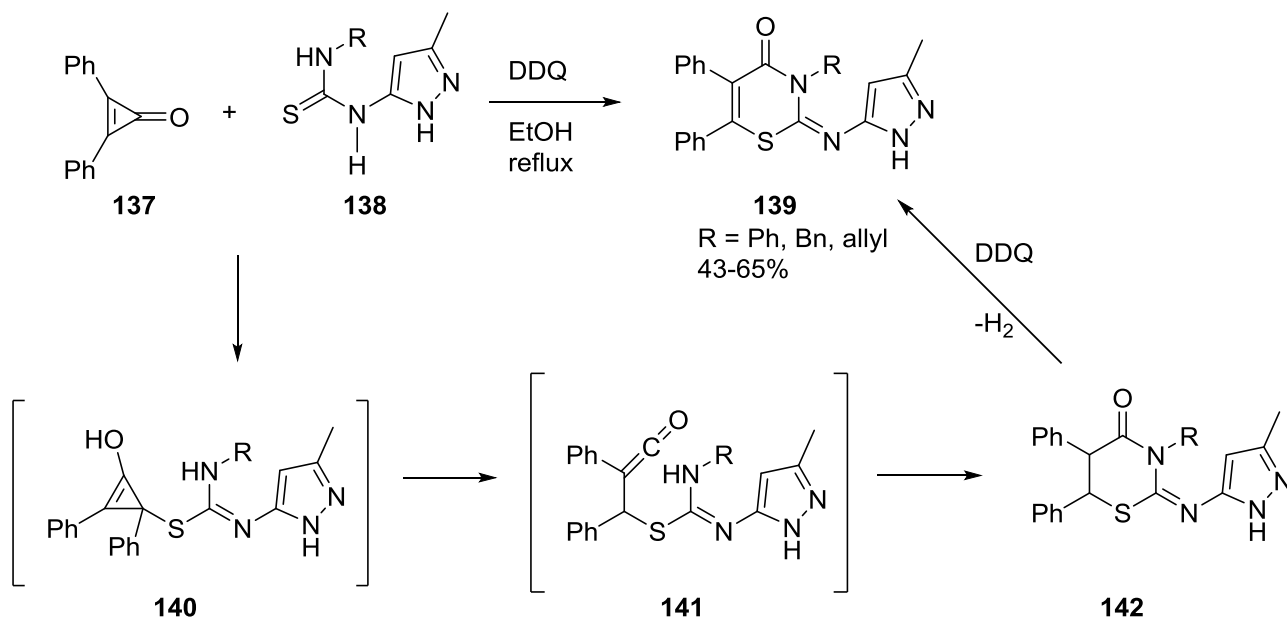
Scheme 40

2-Peptidylimino-2,3-dihydro-1,3-thiazin-4-ones **146** were synthesized from the corresponding 2-thiones **143** (Scheme 41). Treatment of **143** with diethyl sulfate gave isolable salts **144** with a stabilized carbocation. Treatment with dipeptides **145** (gly, gly or gly, L-ala) provided compounds **146**.[83]

R^1 = Ph, *p*-Cl-C$_6$H$_4$
R^2 = Ph, *p*-OMe-C$_6$H$_4$
R^3 = H, Me
76-84%
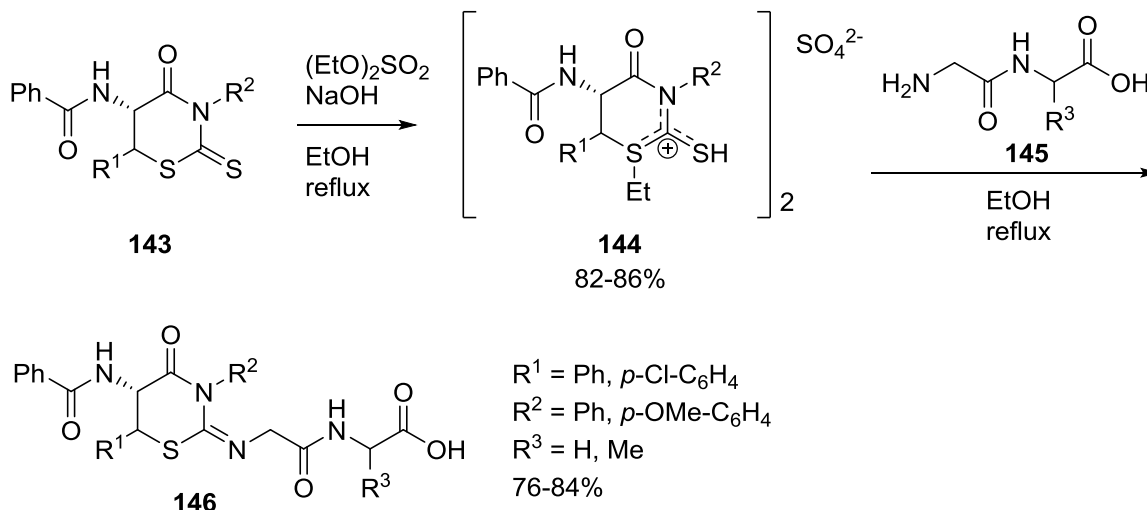
Scheme 41

2.3.6. 2,3-Dihydro-1,3-benzothiazin-4-ones. In the original review, it was stated that the most common method used for the synthesis of 2,3-dihydro-1,3-benzothiazinones **149** was the reaction of 2-sulfanylbenzamides with carbonyl compounds. Since then, however, the most widely used method has been the reaction of 2-sulfanylbenzoic acids **147** with imines **148**, which can be prepared *in situ* (Scheme 42). In the prior review, this was mentioned as a way to prepare *N*-alkyl or *N*-amido 2,3-dihydro-1,3-benzothiazin-4-ones, by refluxing in a solvent. Thermal methods continue to be used. In recent examples, *N*-aryl[84] and *N*-amido[85] compounds were made in refluxing benzene, *N*-amido compounds were prepared in 1,4-dioxane at 100 °C[8] or 130 °C,[86] and *N*-alkyl compounds were synthesized in refluxing toluene.[87,88] Sodium sulfate was used to remove water from the condensation reaction in refluxing dioxane to make one *N*-aryl compound in each of two reports.[88,89] Another report shows Na$_2$SO$_4$ in the graphic, but this is not mentioned in the experimental, where it was stated that the reaction ran at room temperature.[90] There is a claim in the literature that treatment of 2-sulfanylbenzoic acid with molecular sieves dehydrated it to give a thioketene intermediate, which reacted with *N*-benzylideneaniline to give 2,3-diphenyl-2,3-dihydro-1,3-benzothiazin-4-one.[91] However, the ^{1}H NMR data and melting point do not match those reported elsewhere[92-94] which were confirmed by x-ray crystallography.[94]

The reaction has also been catalyzed by TsOH in refluxing toluene (33-73%).[95]
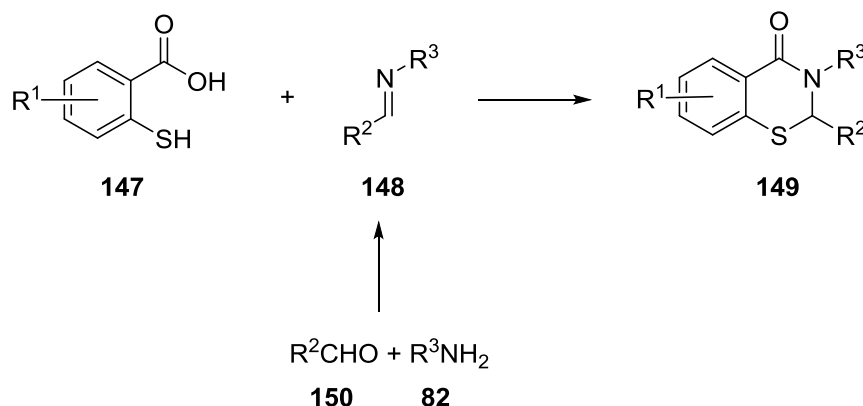
Scheme 42

Highly polarized imines **151** have been used to form 2,2-disubstituted-2,3-dihydro-1,3-benzothiazin-4-ones **152** at room temperature in THF (Scheme 43).[96,97] Scheme 59 shows a similar reaction.
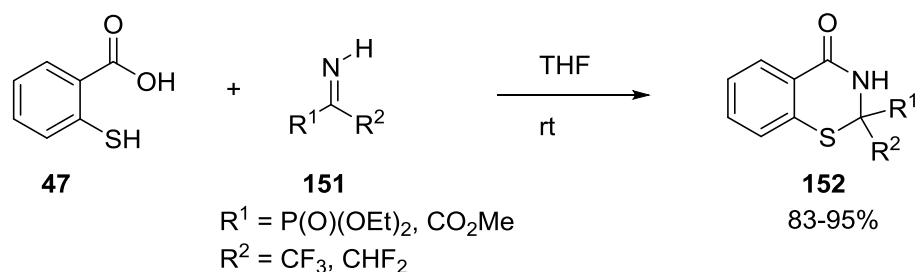
Scheme 43

Microwaves have also been used in this type of reaction and they greatly increased the rate of the reaction (6-8 min vs. 10-13 h thermal) of exocyclic imines **153** in ethanol/acetic acid to give spiro compounds **154** (Scheme 44). Yields were also generally somewhat improved compared to thermal reactions without microwave irradiation (74-81% vs. 65-72%).[98]
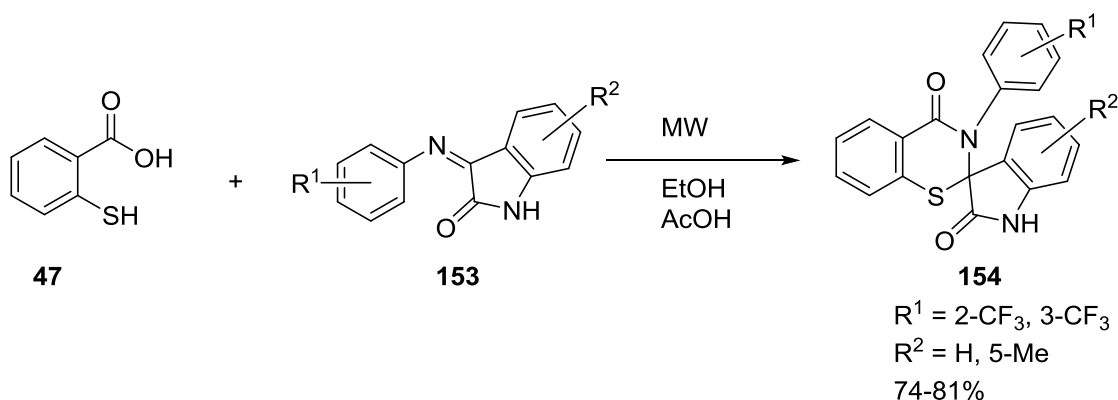
Scheme 44

DCC has been used to activate the acid in three-component reactions. The reaction of amines **155**, aldehyde **156**, and 2-sulfanylbenzoic acid **47** was run in refluxing toluene.[99,100] In another case, an HCl salt of the amine was used. Sodium bicarbonate was included in the reaction to neutralize the HCl, with *N,N*-dimethylaminopyridine (DMAP) as a promoter along with DCC (Scheme 45). The desired 2,3-dihydro-1,3-benzothiazin-4-one **157** was accompanied by **158**, which did not include the amino ester.[101]
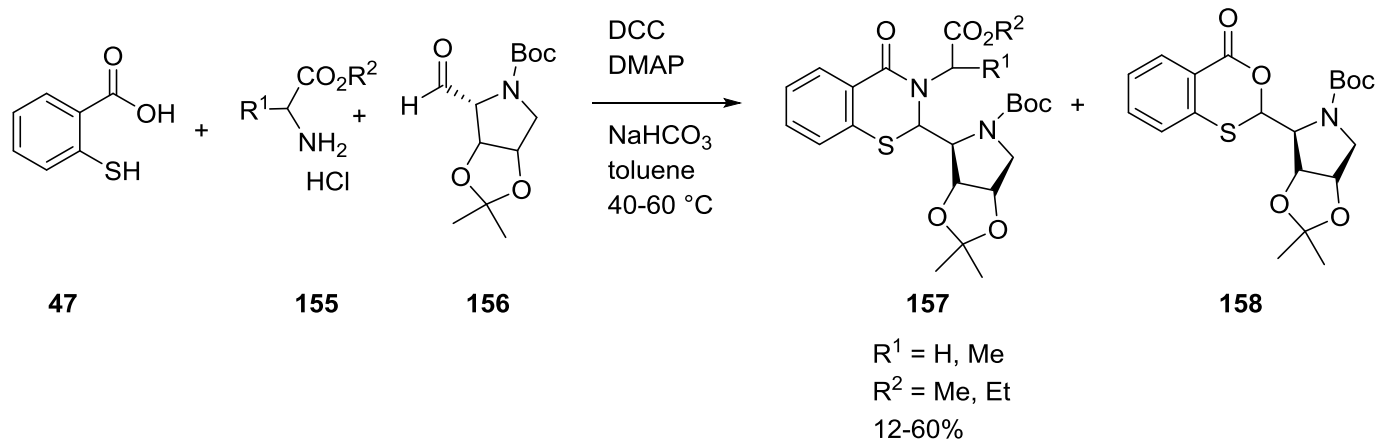
Scheme 45

Another reagent that has been used to activate the carboxylic acid is 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P) **159**, with either pyridine at room temperature,[92-94,102-105] or diisopropylethylamine (DIPEA) at 90 °C.[106,107] The mechanism was proposed to begin with reaction of the acid with T3P **159** to give phosphate intermediate **160**, then attack by the nitrogen on the activated carbonyl to give iminium ion **161**, and then ring closure by attack of the sulfur to produce product **162** (Scheme 46).[106] R^2 can be aryl (13-43%)[92-94,102-105] or methyl (99%).[106,107] R^1 is aryl in these examples, but also see Scheme 106 for cycloalkyl.
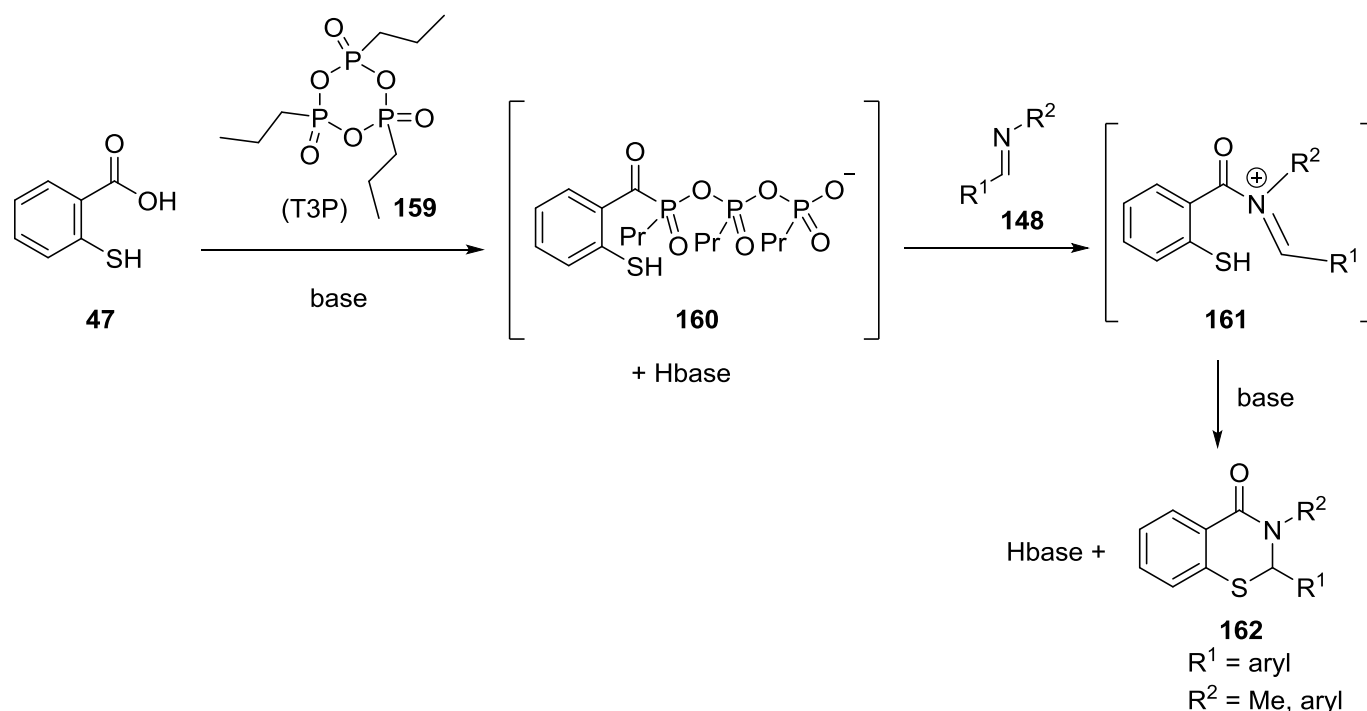
Scheme 46

Methyl 2-sulfanylbenzoate **163** was reacted with ammonia and acetophenone derivative **164** in methanol under microwave irradiation at 150 °C to give the 2-aryl-2-methyl-2,3-dihydro-1,3-benzothiazin-4-one **165** (Scheme 47).[108]
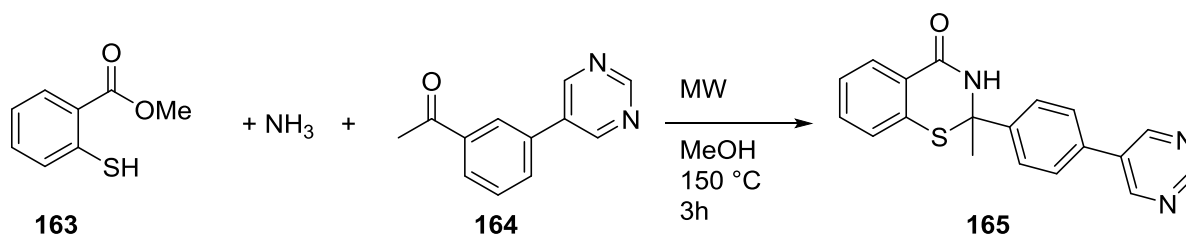
Scheme 47

In the earlier review, the reaction of acetylenic esters with 2-sulfanylbenzamides was discussed. In a recent report, methyl propiolate **167** was reacted with 2-sulfanylbenzamides **166** in the presence of potassium phosphate in refluxing toluene to give products **168** in a one-pot procedure (Scheme 48).[109] The first step was proposed to be 1,4-addition of the thiol to the terminal alkyne, and then the base catalyzed addition of the amide nitrogen to the alkene intermediate. Ester **167** could be replaced with an acetylenic ketone or amide, and could also be an internal alkyne.[109]
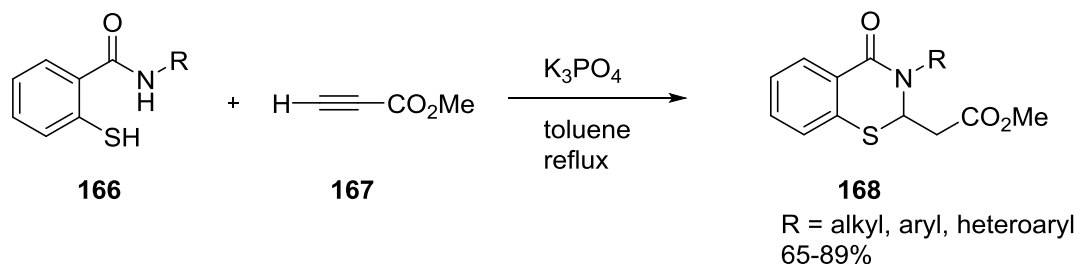
Scheme 48

Photoisomerization of 1,2-benzothiazine 1,1-dioxides **169**, including the non-steroidal anti-inflammatory drug (NSAID) piroxicam, has been shown to produce the 2,3-dihydro-1,3-benzothiazin-4-one compounds **170** (Scheme 49).[110]
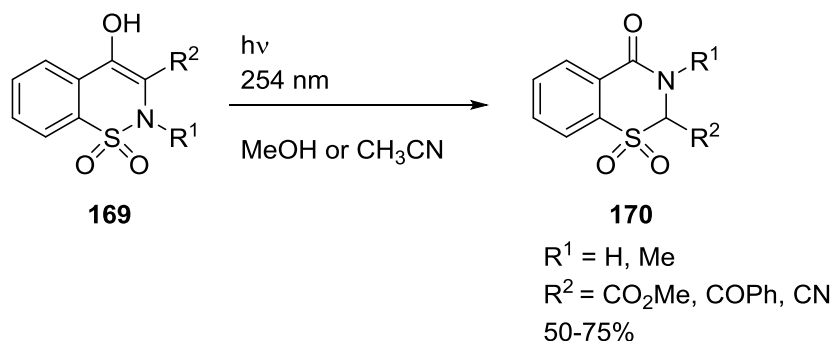
Scheme 49

1,3-Benzothiazin-4-ones **171** (see Section 2.2.1) were converted into 2,3-dihydro-1,3-benzothiazin-4-ones **172** by reduction of the C=N bond using sodium borohydride in ethanol (Scheme 50).[13]
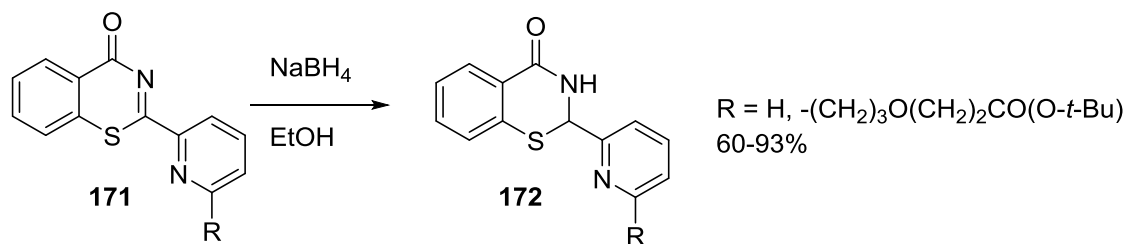
Scheme 50

2.3.7. 2,3,5,6-Tetrahydro-1,3-thiazin-4-ones with an exocyclic C=C. Condensation of thioamide **174** with 3-(4-nitrophenyl)-2-propenoyl chloride **173** was reported to produce the 2,3,5,6-tetrahydro-1,3-thiazin-4-one **60**, with an exocyclic C=C double bond at C2, in a 1:1 mixture with lactam **175** (Scheme 51).[33] The 1,3-thiazin-4-one was only formed in this specific case; different products were obtained, depending on the substituents on the thioamide and the propenoyl chloride. The authors suggested that in the presence of K₂CO₃ the nitrogen in **174** attacked the carbonyl in **173**, giving an intermediate amide, which then converted to the two products. However, only one product was formed when phenylsulfonylthioamides **177** were reacted with 3-phenyl-2-propenoyl chloride **176** (Scheme 52).[111]
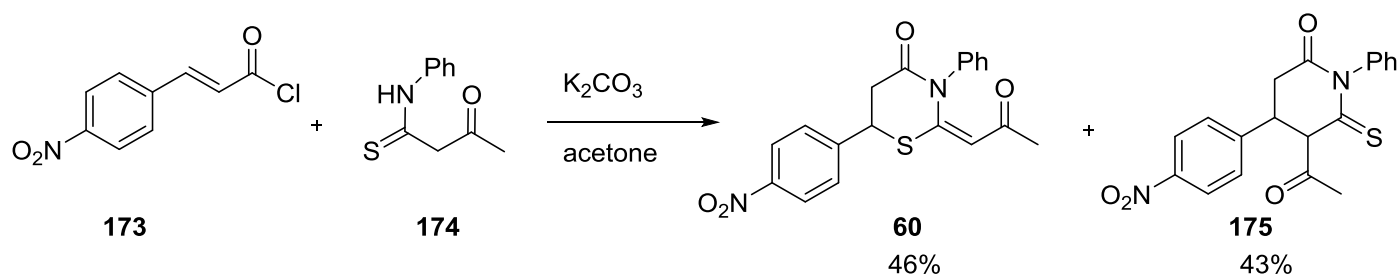
Scheme 51
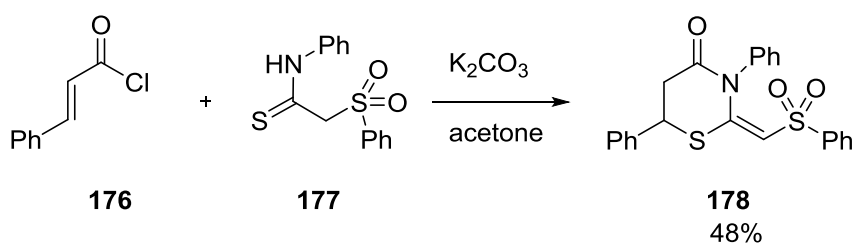
Scheme 52

A different approach to a 2-alkylidene compound started with 2,4-dihydropyrazol-3-one **179,** which had an active methylene which was deprotonated with sodium hydride and reacted with phenyl isothiocyanate **107** to yield the sodium salt of the enethiol form of thioamide **180**. Addition of ethyl 3-bromopropanoate **85** to the reaction mixture yielded the product **181** (Scheme 53).[112]
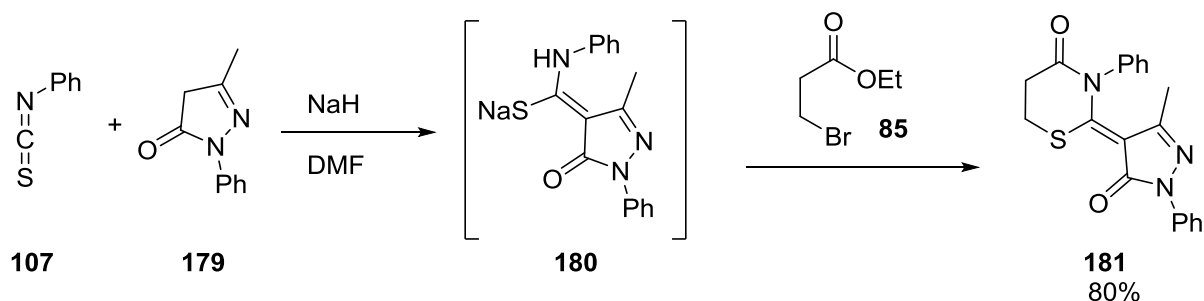
Scheme 53

In a similar vein, the active methylene in α-cyanoacetamides **182** was deprotonated with KOH and reacted with phenyl isothiocyanate **107**, then acidified to give the isolated thioamide tautomers **183**. Treatment with 3-chloropropanoyl chloride **95** and triethylamine afforded the 2-alkylidene products **184** (Scheme 54).[113]
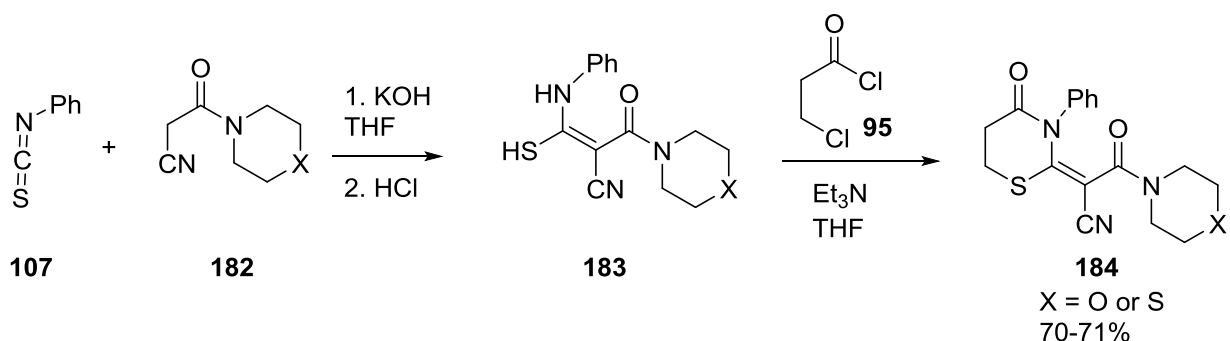
Scheme 54

Ethyl 3-sulfanylpropanoate **185** reacted with malononitrile **6** with catalytic potassium carbonate in ethanol to give **186**.[114] Under thermal conditions the yield was only 3%, but with microwave irradiation, a 27% yield was achieved (Scheme 55).[114]
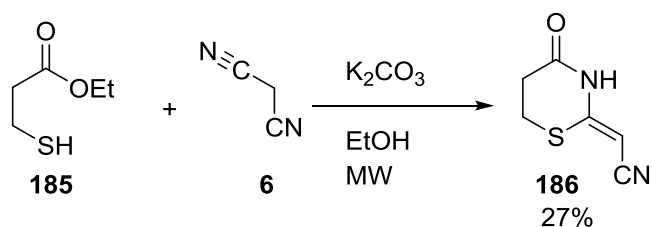
Scheme 55

2.3.8.   2,3,5,6-Tetrahydro-1,3-thiazin-4-ones. The most commonly used method for the preparation of 2,3,5,6-tetrahydro-1,3-thiazin-4-ones **189** has been the combination of a 3-sulfanylpropanoic acid **187** and an imine **188**, which can be prepared *in situ* (Scheme 56).
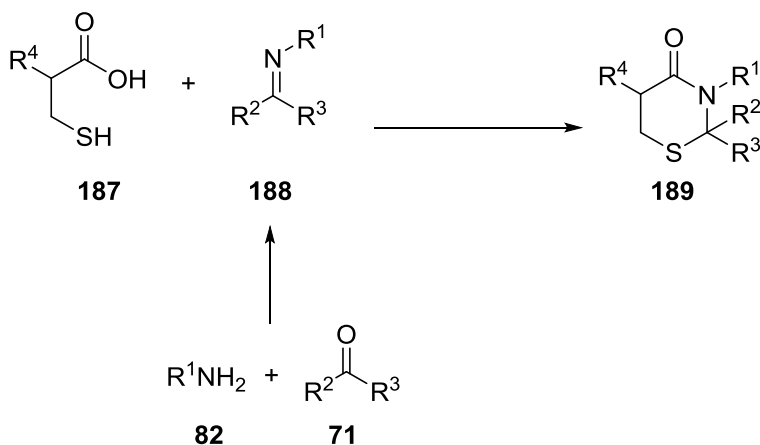
Scheme 56

Some compounds were prepared just by heating, as reported in the previous review. Usually this has been done in benzene or toluene. In a recent report, one example was carried out as a three-component reaction at 120 °C without a solvent.[115] In one case, it was shown that at room temperature in toluene the product **192** formed was the result of attack by the sulfur on the imine carbon. Upon heating to reflux, the amide bond formed (Scheme 57).[116]
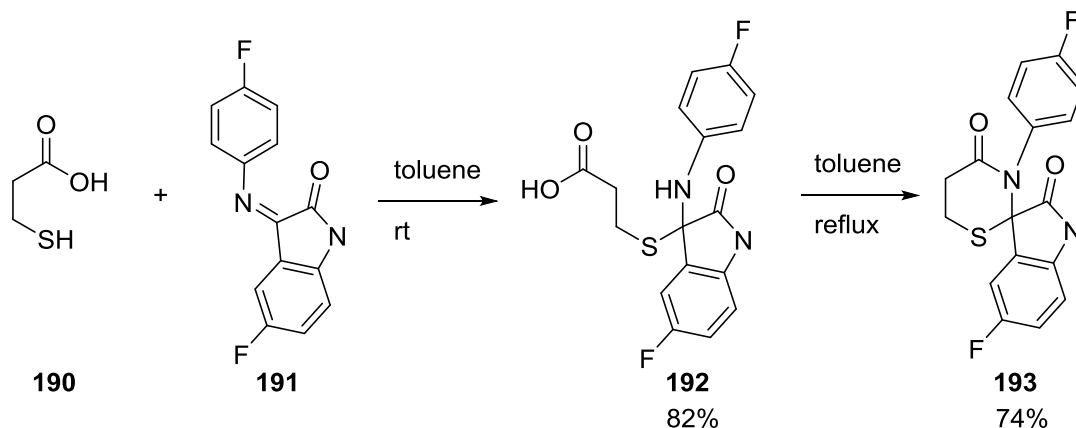
Scheme 57

Pyridine was used as solvent for the reaction of 4-aminocoumarin **195** with benzaldehyde **194** and 3-sulfanylpropanoic acid **190** (Scheme 58). The authors suggested imine formation was followed by conjugate addition of the sulfur and then amide formation. The role of pyridine was not commented on.[117]
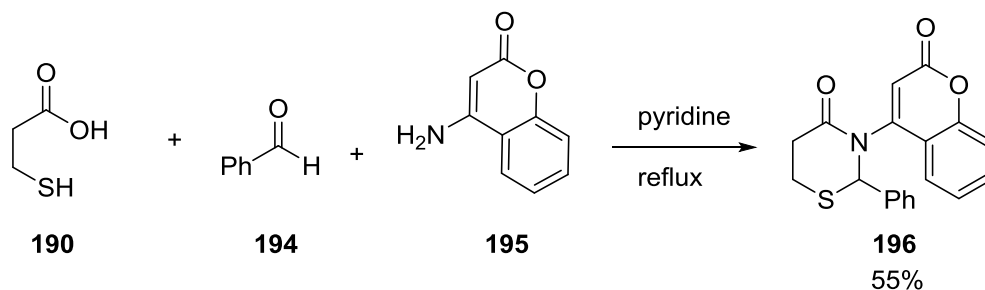
Scheme 58

Highly polarized imines **151** have been used to form the 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones **197** at room temperature in benzene[96] or ether (Scheme 59).[97] Scheme 43 shows a similar reaction.

R^1 = P(O)(OEt)$_2$, CO$_2$Me
R^2 = CF$_3$, CHF$_2$
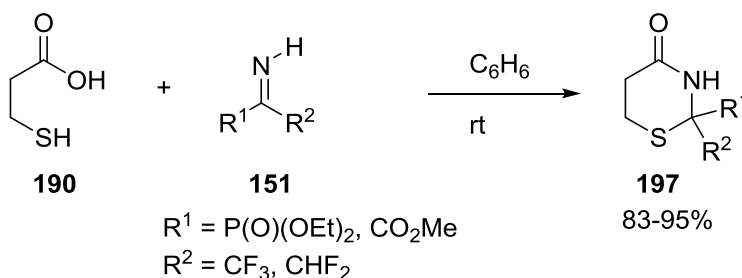
Scheme 59

More commonly, since the last review, a catalyst or promoter has been used.

Many investigators have used reagents that activate the carboxylic acid to promote amide formation. These include carbodiimides DCC,[4,12,87,100,118-123] diisopropylcarbodiimide (DIC),[124,125] and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC);[3,126,127] thionyl chloride,[128] *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU)/DIPEA,[129] and T3P **159** with pyridine[93,130-132] or DIPEA.[133] Most of the reports used aldehydes, but two of them used ketones.[120,128] T3P **159** has been shown to work with *N*-acetylcysteine as the thioacid.[93,117,133]

Acid catalysis has also been used. Acids used include ZnCl$_2$[134] and TsOH.[135] Trifluoroacetic acid has been used to catalyze a reaction using an oxime **198** instead of an imine (Scheme 60).[136]
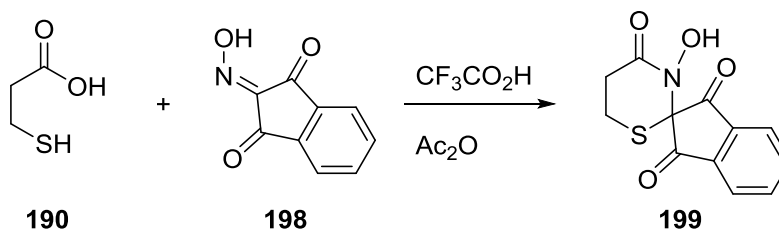
Scheme 60

The effect of ultrasound on three-component reactions has been investigated. In one study, reactions were carried out either in refluxing toluene, or at room temperature in toluene with ultrasound. Yields were somewhat lower with ultrasound (41-88% vs. 41-97%), but the reactions were substantially faster (25 min. *vs.* 19 h).[137] Another group found optimal conditions for their reaction when a polyethylene glycol (PEG)-OSO$_3$H catalyst was used in combination with ultrasound in water (Scheme 61). PEG-OSO$_3$H acted as both an acid catalyst and a phase transfer catalyst.[138] Reactions under these conditions ran to completion in 20-38 min. with 85-89% yields.
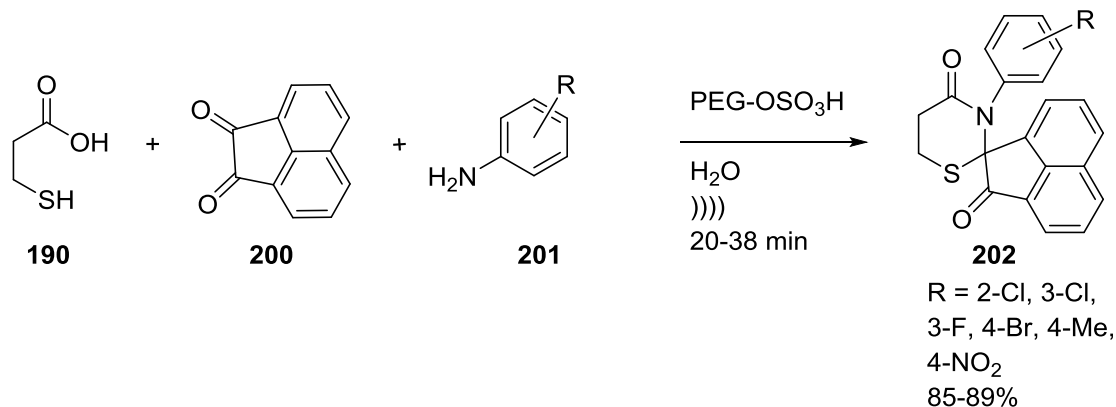
Scheme 61

Microwaves have also been used in this reaction and they greatly increased the rate (11-17 min. vs 13-20 h) and more modestly the yields (68-82% vs. 14-68%) in ethanol (Scheme 62).[139] The MW reactions were run for only 2-4 min. in the acidic ionic liquid 1-methylimidazolium tetrafluoroborate ([MIM]$^+$BF$_4^-$) at 140 °C, giving excellent yields of spiro compounds **204** (90-97%).[140] Alternatively, the reactions were run without solvent using acidic solid montmorillonite KSF as a support while irradiating (6-8 min., 75-93%).[141]
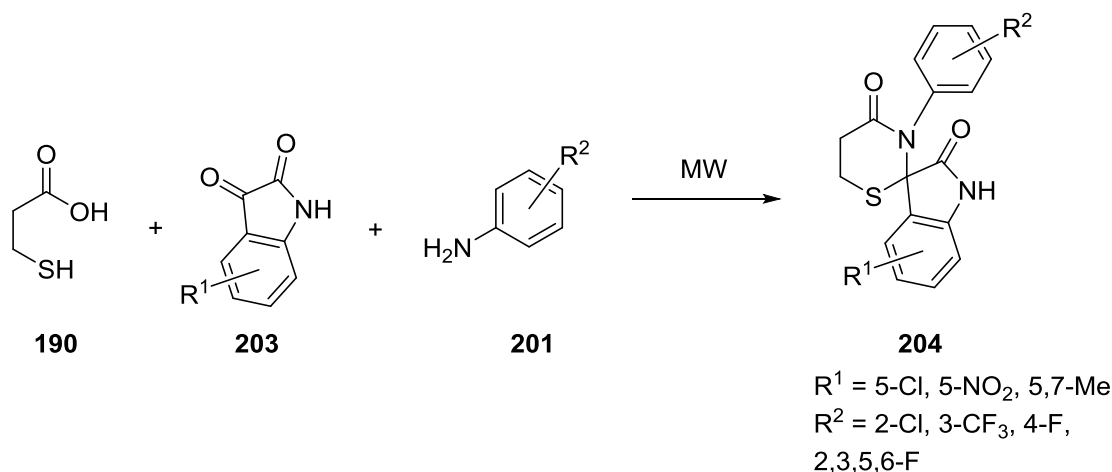
Scheme 62

Reaction of enones **205** with excess 3-sulfanylpropanoic acid **190** and ammonium carbonate gave addition of two equivalents of the acid, with one cyclizing with a nitrogen to give the 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones **206** (Scheme 63). No mechanism was proposed.[142]
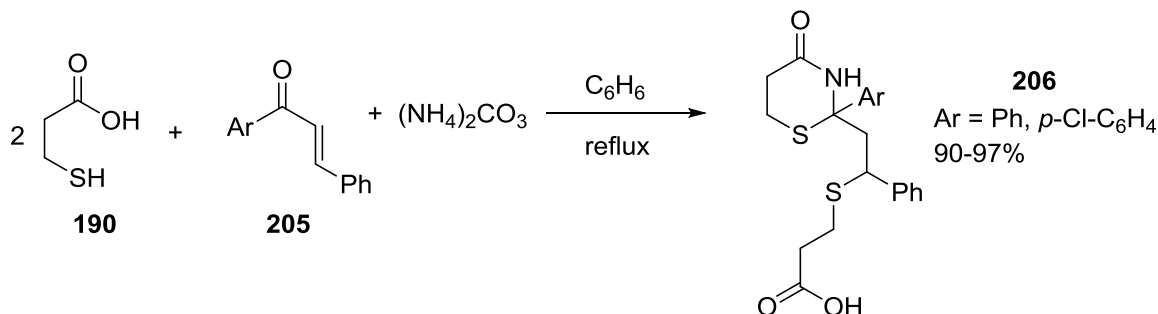
Scheme 63

Reaction of 3-mercaptopropanamide **207** with aryl methyl ketones **208** with TsOH catalyst in refluxing toluene produced 2,2-disubstituted-2,3,5,6-tetrahydro-1,3-thiazin-4-ones **209** (Scheme 64).[108]
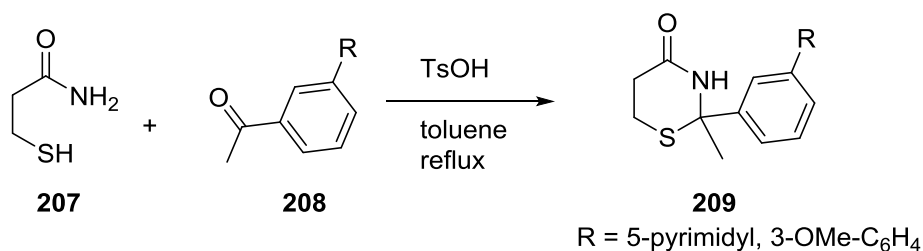
Scheme 64

The reaction of thioamides **8** with ethyl acrylate **210** in the presence of boron trifluoride in toluene produced the 2-ethoxy-2-fluoroalkyl-2,3,5,6-tetrahydro-1,3-thiazin-4-ones **213**. Presumably, the reaction initially produced the 5,6-dihydro compound **212**, but addition of ethanol to the C=N unit gave **213** (Scheme 65).[143]
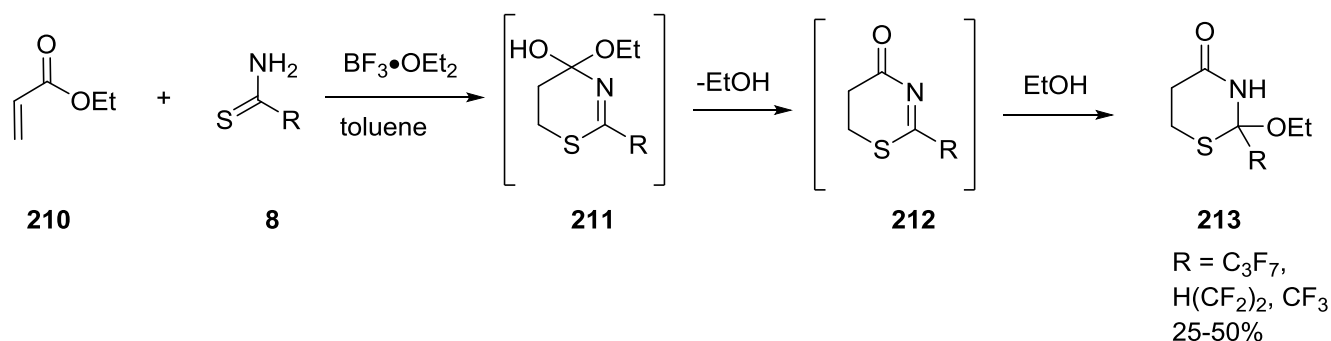
Scheme 65

2.4. 1,3-Thiazin-4-ones with fused heterocycles

2.4.1. *e*-Fused 1,3-thiazin-4-ones. As part of a synthesis of the natural product cyclobrassinone, *t*-butoxycarbonyl (Boc)-activated isothiocyanate **214** was reacted with methanol in acetone to produce the monothiocarbamate **216**. Addition of triethylamine to the reaction mixture induced cyclization by aromatic substitution of the indole chlorine atom to give the desired indole-fused **217** (Scheme 66).[144,145] Other examples were also demonstrated in which methanol was replaced with ethanol or isopropanol (47-64% from **214**).[145]
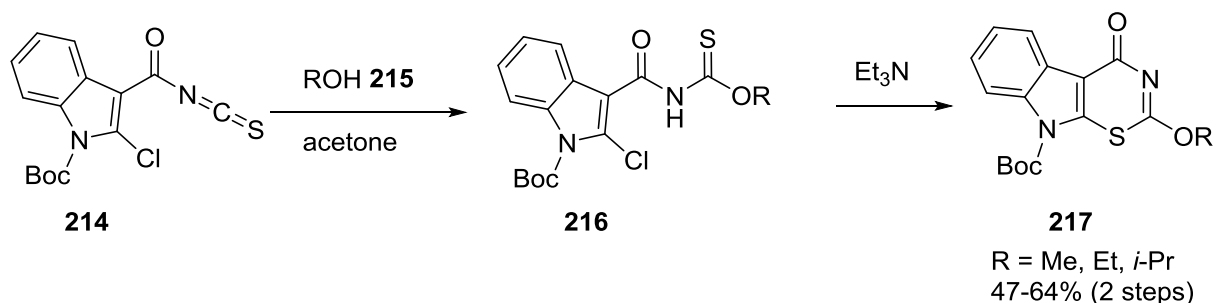
Scheme 66

From compounds **218**, analogous to **216** but where the indole nitrogen bears an alkyl or alkoxy substituent rather than the activating Boc group, cyclization under known conditions such as NaH, LiH, Et$_3$N, NaOMe, and heat failed. Cyclization was ultimately achieved photochemically (Scheme 67).[145] A similar reaction is shown in Scheme 73.

217   **218**   **219**
21-42%   R^1 = Me, Bn, 4-OMe-C$_6$H$_4$
R^2 = Me, Et, *i*-Pr
33-55%
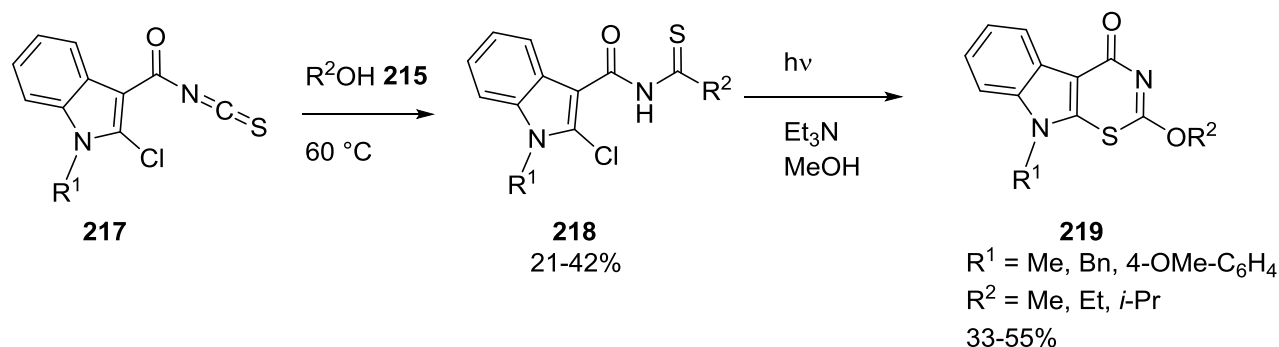
Scheme 67

When α-arylhydrazonomalononitriles **221** were combined with 2-keto-3-sulfonylcinchonic acid derivatives **220**, the reactions were run in refluxing acetic acid.[146] It was suggested that the sulfur attacked one of the nitrile groups to give thioamide intermediates **222**, which cyclized to form products **223** (Scheme 68).

220   **221**   **222**   **223**
R^1 = H, Me
R^2 = H, 4-Me, 4-OMe, 4-Cl
58-67%l
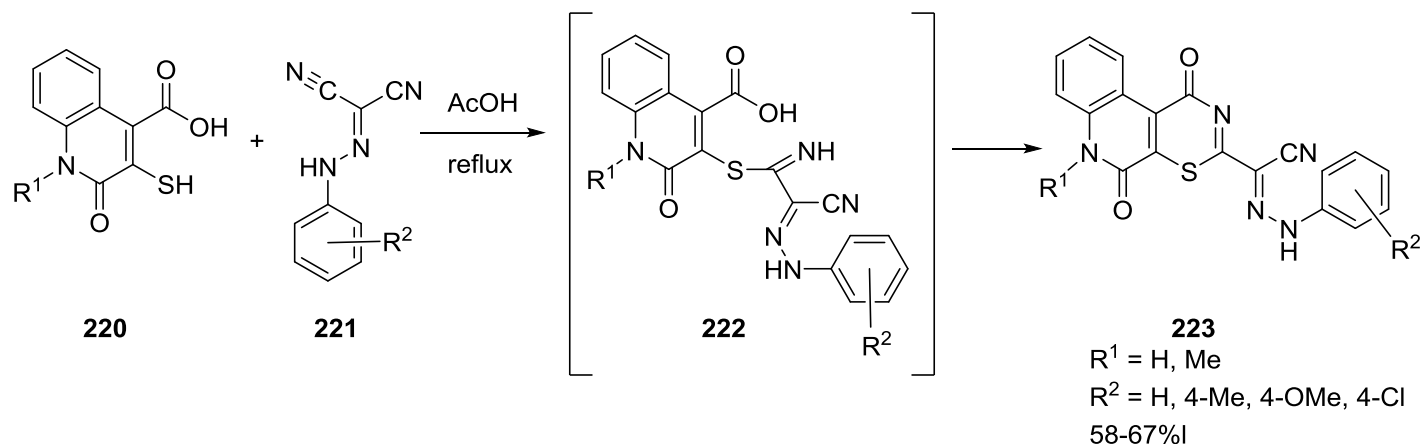
Scheme 68

Methyl 2-sulfanylpyridine-3-carboxylate **224** has been reacted with aryl nitriles **33** in the presence of pyridine to give two 1,3-pyridothiazin-4-ones **225** in poor yield (Scheme 69).[13] This is similar to the 1,3-benzothiazin-4-one preparations in Scheme 10.

224   **33**   **225**
Ar = 2-pyridyls
1-10%
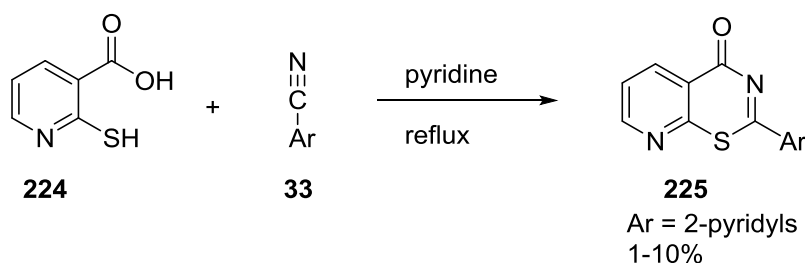
Scheme 69

2.4.2. *e*-Fused 2-imino or 2-amino derivatives of 1,3-thiazin-4-ones. To prepare 2-imino-1,3-pyridothiazin-4-one **231**, 4-chloropyridine-3-carboxylic acid **226** was converted into the acid chloride **227**, which was reacted with ammonium thiocyanate to give the isothiocyanate **228**. Treatment with *N*-methyl-*N*-(4-chlorophenyl)amine **229** gave the substituted thiourea **230** and cyclization took place in the room temperature acetone solution (Scheme 70).[28] This is similar to prior art using 2-chloropyridine-3-carboxylic acid.
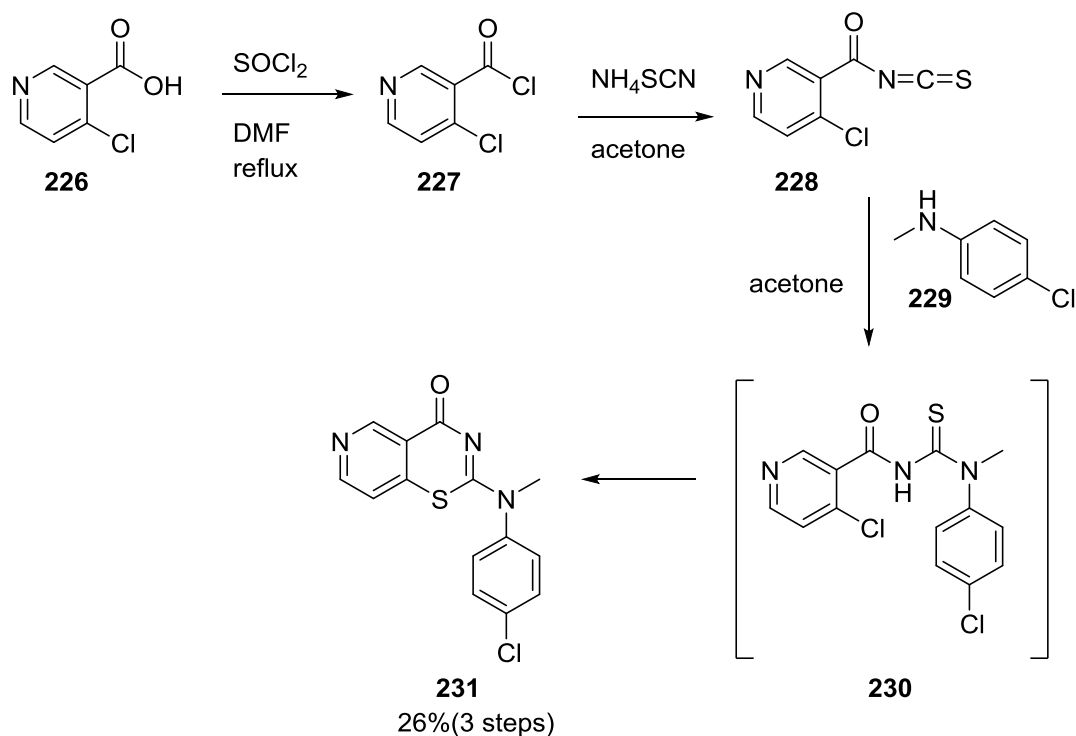
Scheme 70
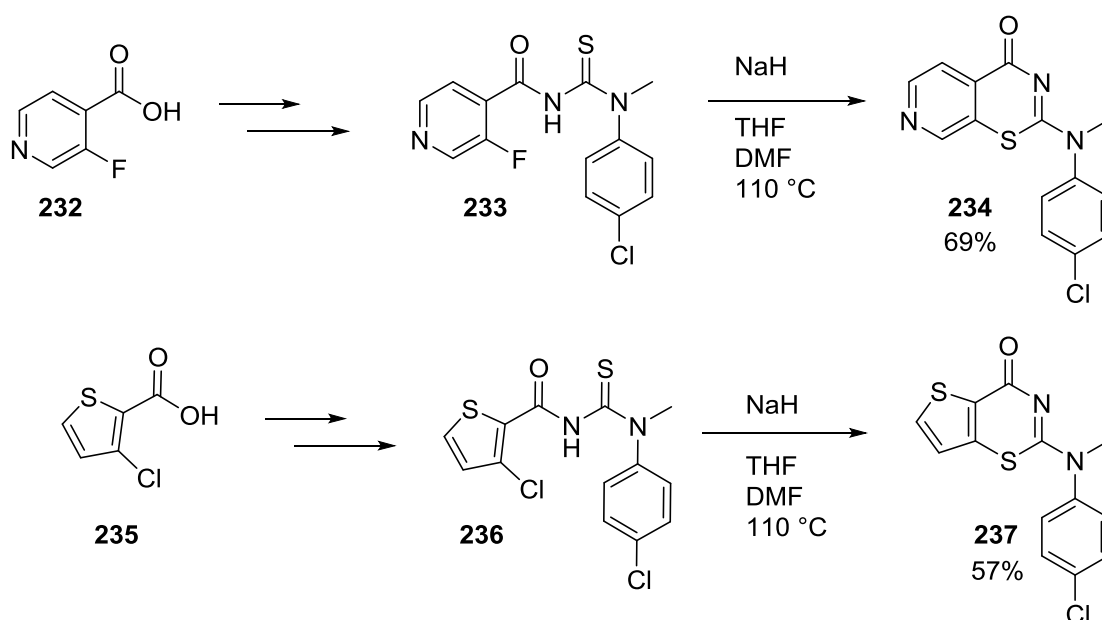
Scheme 71

Starting with 3-fluoropyridine-4-carboxylic acid **232**, the cyclization step was performed using sodium hydride in DMF and THF at 110 °C. This also succeeded starting with 3-chlorothiophene-2-carboxylic acid **235** (Scheme 71).[28]

In chemistry similar to Scheme 66, amines were added to indole isothiocyanate **214**, yielding monothiocarbamates **238.** Cyclization of the Boc-activated compound took place with addition of triethylamine in refluxing acetone to give indole-fused products **239** (Scheme 72).[145]
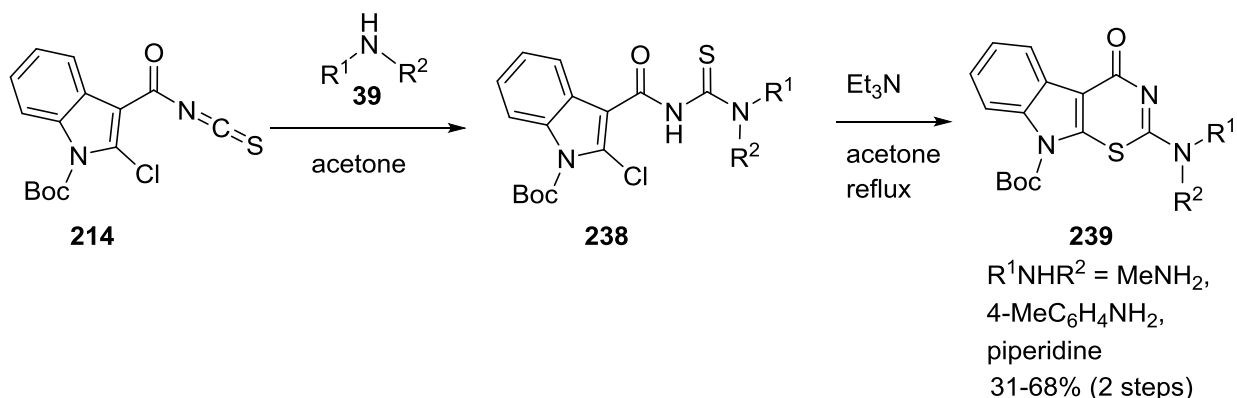
Scheme 72

As in Scheme 67, cyclization of compound **242** under known conditions such as NaH, LiH, Et$_3$N, NaOMe, and heat failed. Cyclization was again achieved photochemically (Scheme 73).[145]
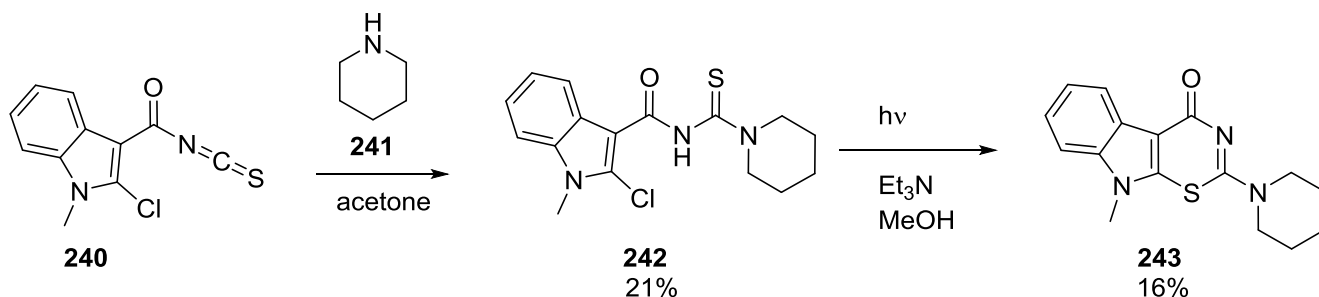
Scheme 73

Instead of conversion of 2-chloropyridine-3-carboxylic acid chloride **244** into the isothiocyanate, the amides **245** were first formed. Then reaction with sodium hydride and an aromatic isothiocyanate **246** in DMF directly gave the 1,3-pyridothiazin-4-ones **247.** The mechanism was proposed to go through the thiourea derivatives **248** (Scheme 74).[147]
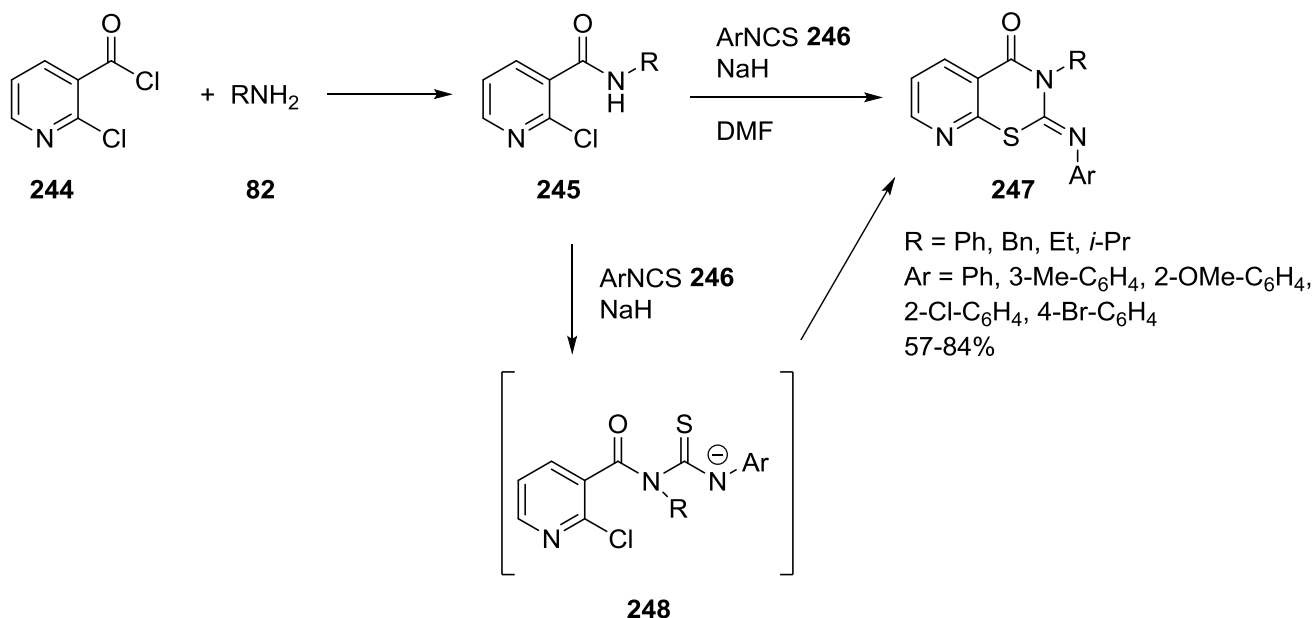
Scheme 74

2-Sulfanylpyridine-3-carboxylic acid **224** was reacted with the *N*-cyanoacetamide **249** in *N,N*-dimethylacetamide (DMAC) at 100 °C to yield the 1,3-pyridothiazin-4-one **250** in low yield (Scheme 75).　In this case, a thiourea intermediate was presumed to form from attack of the thiol of **224** on the nitrile of **249** to give intermediate **251**, which cyclized to give **250**. This only worked with **249**; less electrophilic cyanamides did not react with the thiol of **224**, which was less nucleophilic than in 2-sulfanylbenzoic acid **47**.[31]
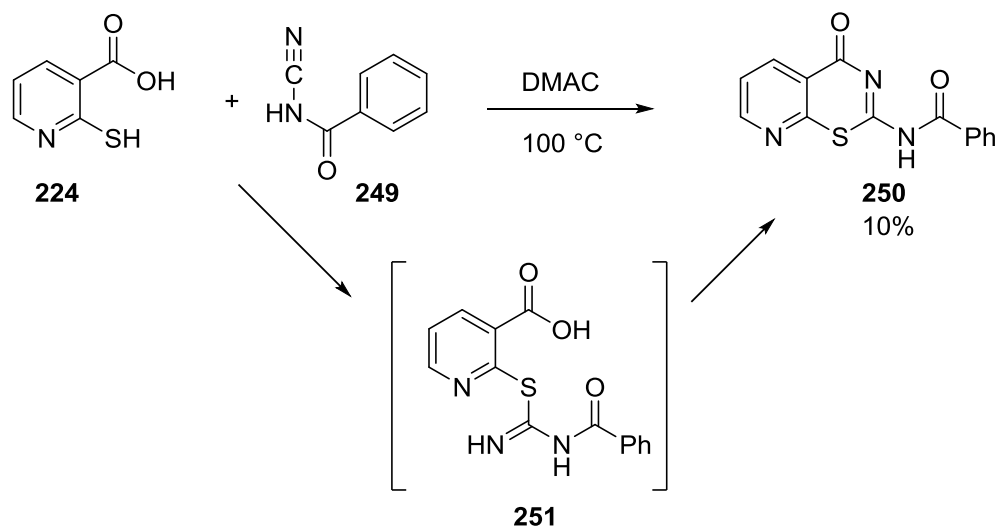
Scheme 75

2.4.3.　*e*-Fused 2,3-dihydro-1,3-thiazin-4-ones.　2-Keto-3-sulfanylcinchonic acid derivatives **252** reacted with diaryl aldimines **253** in refluxing toluene to give products **254** (Scheme 76).[146]
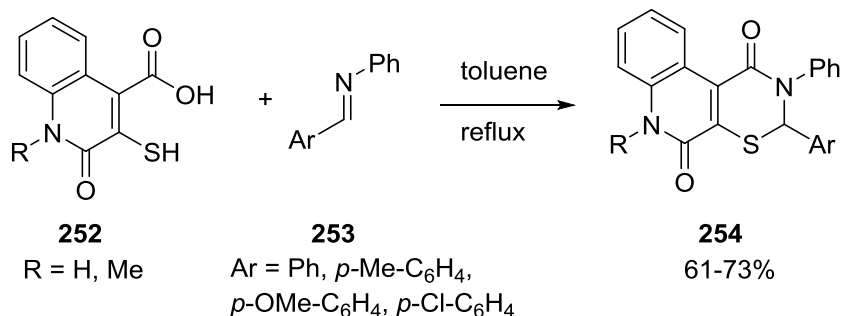
Scheme 76

T3P **159** has been used to synthesize 2,3-dihydro-1,3-pyridothiazin-4-one **256** by the reaction of 2-sulfanylpyridine-3-carboxylic acid **224** with *N*-benzylideneaniline **255** (Scheme 77).[93,148] This is analogous to reactions to prepare 2,3-dihydro-1,3-benzothiazin-4-ones and 2,3,5,6-tetrahydro-1,3-thiazin-4-ones (see Sections 2.3.6 and 2.3.8).
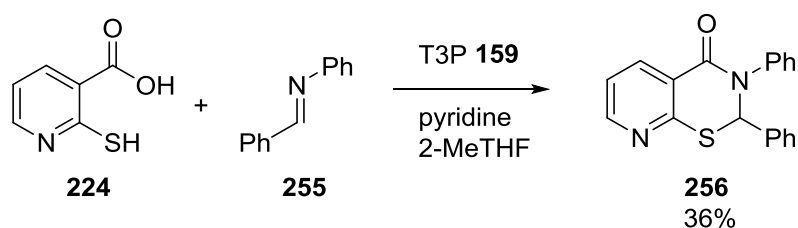
Scheme 77

Zeolite-supported acidic ionic liquid ZSM-5-([MIM]$^+$BF$_4^-$) and sonication were used in a three-component reaction to give 2-spiro-2,3-dihydro-1,3-pyridothiazin-4-ones **258** (Scheme 78).[6,149] It was proposed that the reaction mechanism involved diradical intermediates.[149]
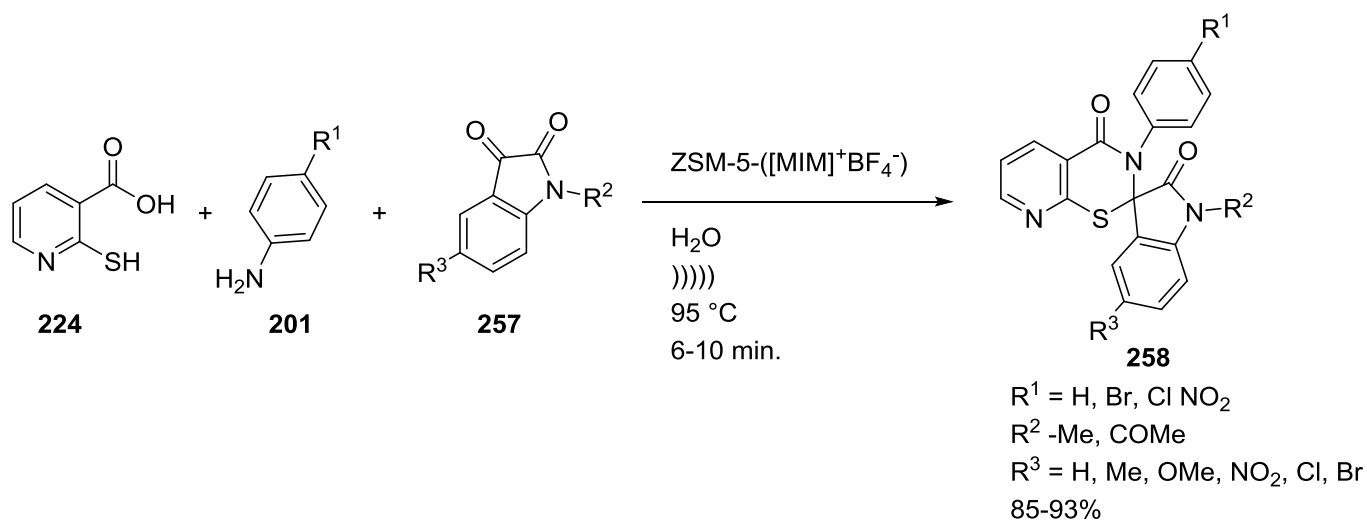
Scheme 78

Microwaves were used in a similar three-component reaction (Scheme 79).[150] Under thermal conditions (DMF, 140 °C, 8 h), there was no reaction between the imine **260** and 2-sulfanylpyridine-3-carboxylic acid **224**.
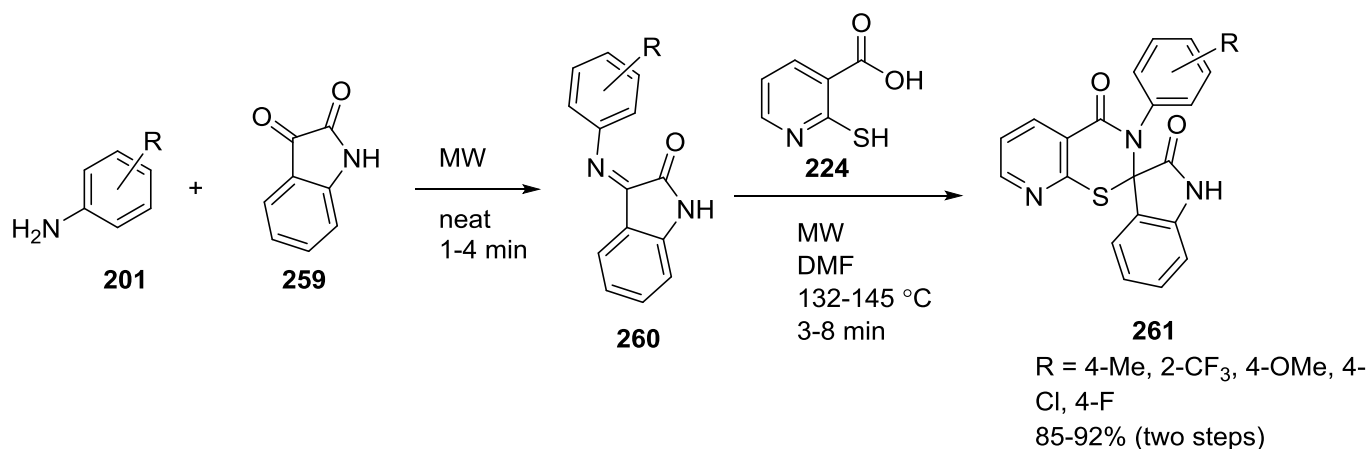
Scheme 79

A novel two-step process was used in the preparation of 2,3-dihydro-1,3-pyridothiazin-4-one **265** (Scheme 80).[151] In the first step, cyclic alkene **262** was reacted with monothiomalonodiamide **263** under basic conditions to yield cyclic thioamide **264**. Treatment with acetone and catalytic conc. HCl yielded **265**. The authors suggested that **262** underwent an S_NVin reaction in which the α-carbon of monothiomalonodiamide **263** displaced morpholine, then cyclization by nucleophilic attack of the thioamide nitrogen on the ketone gave **265**.
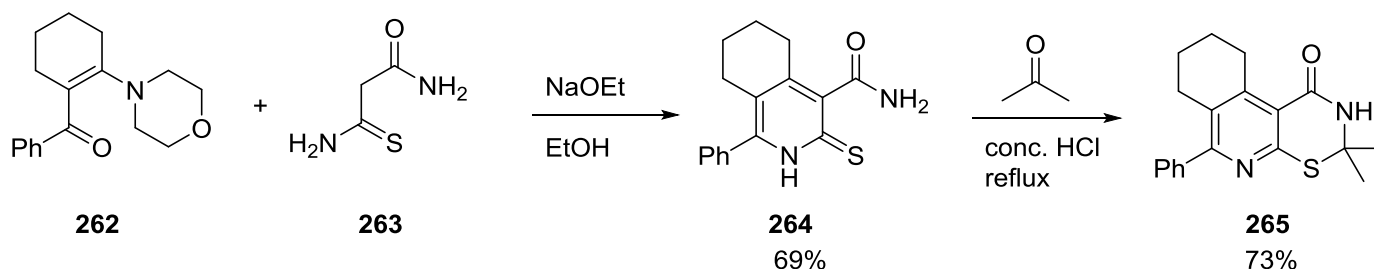
Scheme 80

2,3-Dihydro-1,3-pyridothiazin-4-one **267** was prepared by a Schmidt rearrangement when compound **266** was treated with sodium azide and catalytic sulfuric acid in refluxing DMF (Scheme 81).[152]
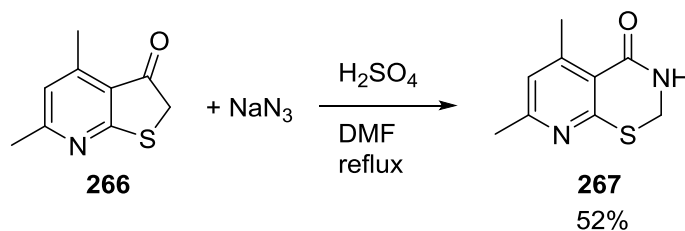
Scheme 81

2.4.4. *e*-Fused 2-imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones.

A novel four-component coupling strategy for preparation of thiosugar-fused 5,6-dihydro-1,3-thiazin-4-ones **270** has been reported. In the reaction, a sugar **268**, masked sulfanylacetic acid equivalent **115**, an amine **82**, and the ionic liquid [bmim]SCN **269** were stirred with a few drops of water (Scheme 82, stereochemistry not shown for simplicity).[153] A possible pathway involved a) tandem Knoevenagel-hydrothiocyanation of **268** by **115** and thiocyanate ion to give nitrile intermediates **271**; b) attack by the amine **82** to give intermediate **272**; c) intramolecular attack by nitrogen on the carbonyl leading to loss of acetophenone and formation of the 1,3-thazin-4-one ring **273**; d) rings closure by cyclodehydration to yield the cyclic thioethers **270**.
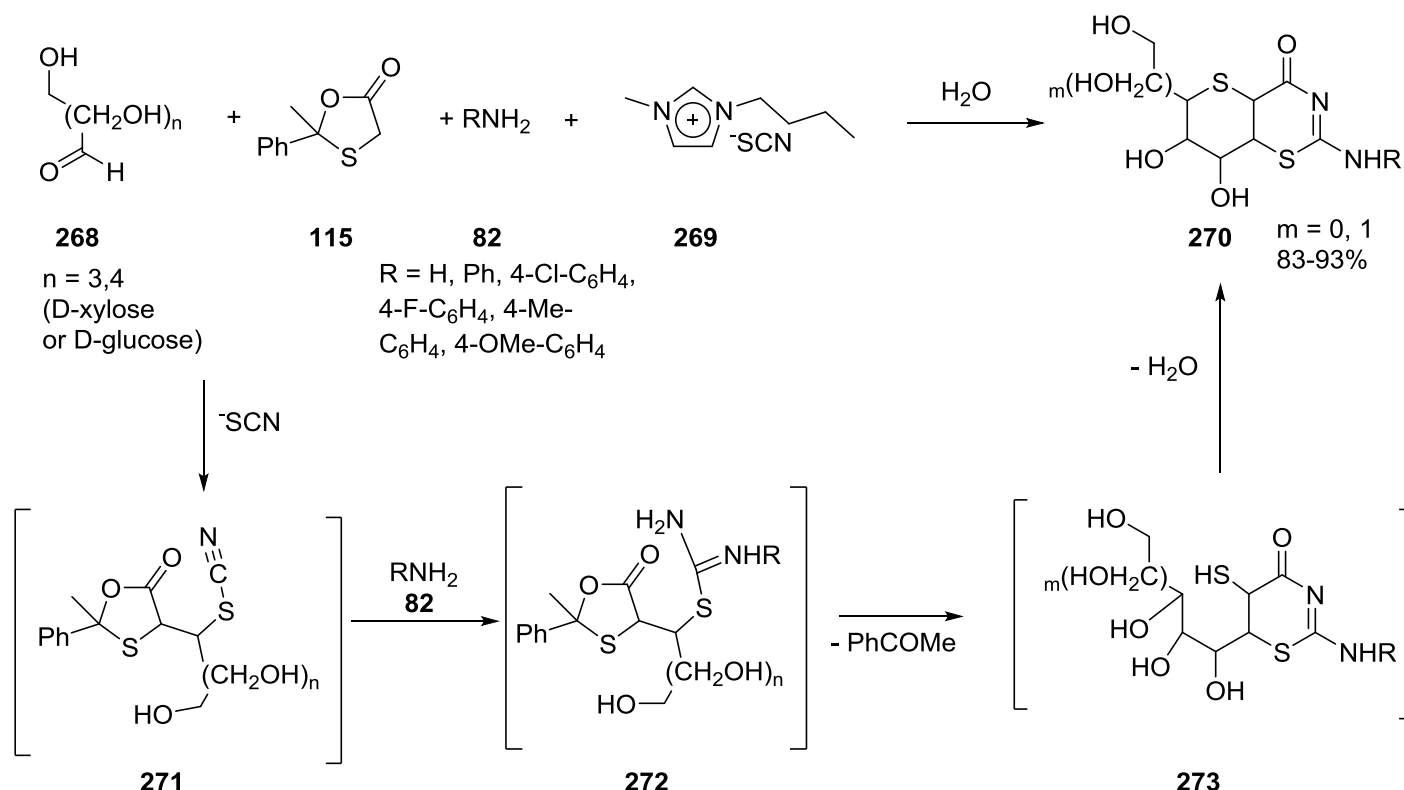
Scheme 82

Recently, a similar reaction was reported, except **115** was replaced with a nitrogen-containing ring, compound **114** (Scheme 83).[154]
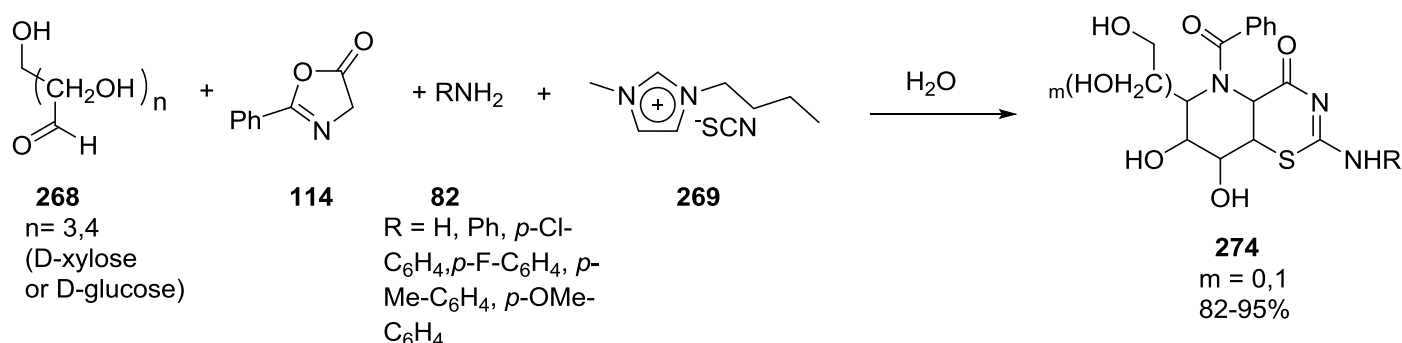
Scheme 83

2.4.5. *b*-Fused 2-imino or 2-amino derivatives of 1,3-thiazin-4-ones. The reaction of cyclic thioureas **276** with *gem*-cyanoester epoxides **275** delivered the *b*-fused 1,3-thiazin-4-ones **277** (Scheme 84).[155] It was proposed that the reaction began with regioselective attack by sulfur on the epoxide, followed by elimination of HCN, and finally intramolecular nucleophilic acyl substitution.
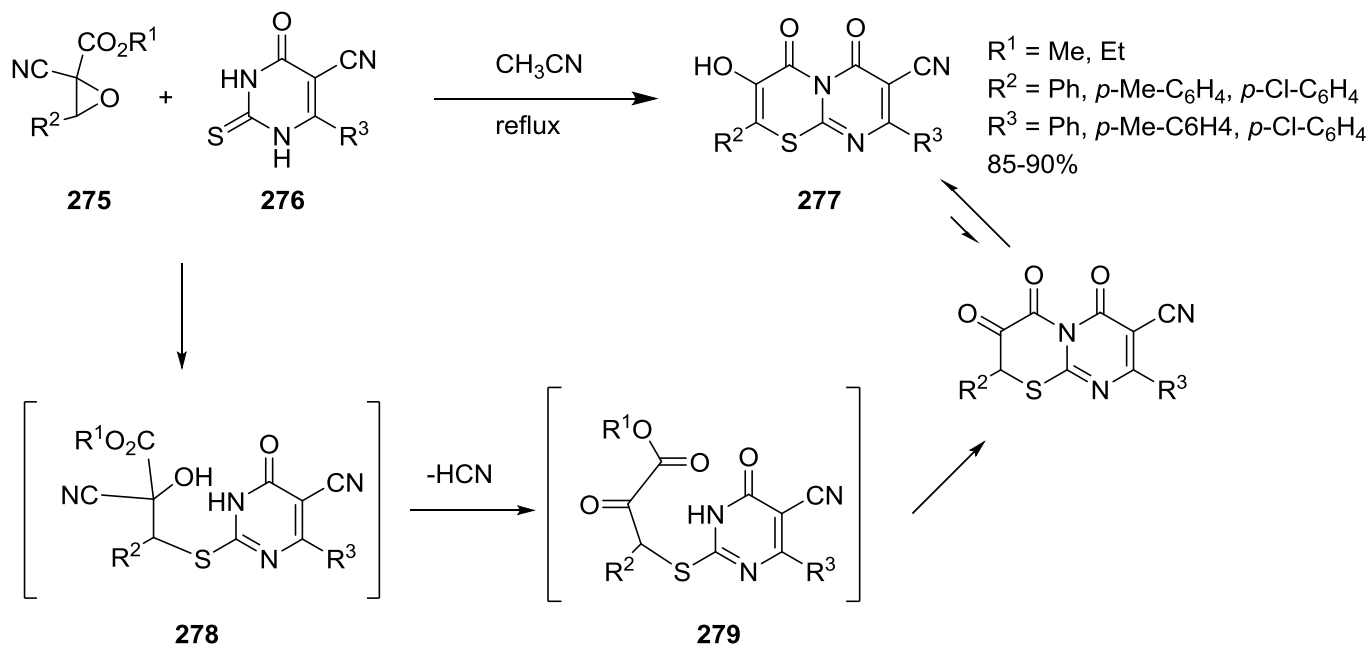
Scheme 84

The *b*-fused triazolo-1,3-thiazin-4-ones **282** were prepared using conjugate addition to acetylenic esters **280** (Scheme 85).[156]
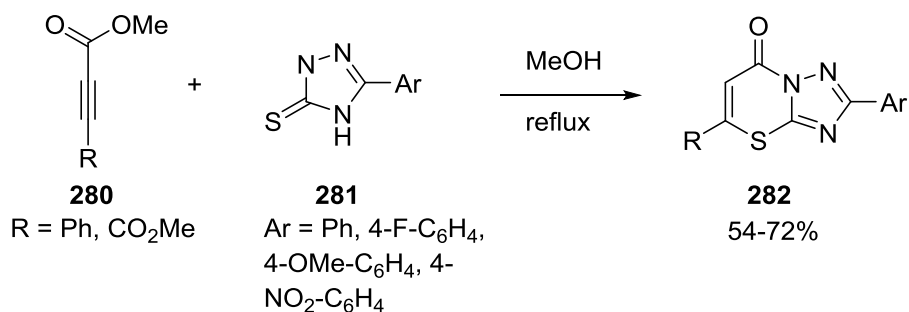
Scheme 85

b-Fused imidazo-1,3-thiazin-4-ones **285** were synthesized by a palladium-catalyzed tandem amino-carbonylation-cyclization reaction (Scheme 86). Imidazoles **283** were treated with $PdI_2/KI/CO/O_2$ (air)/R_2NH/CH_3CN at 100 °C. It was proposed that in the first step, the terminal alkyne was aminocarbonylated to produce the alkynyl amide intermediates **284**. This then went through a second catalytic cycle that effected cyclocarbonylation to **285**.[157] Two carbon monoxides became incorporated into the molecule. The oxygen served to oxidize Pd(0) to Pd(II) in the first catalytic cycle.
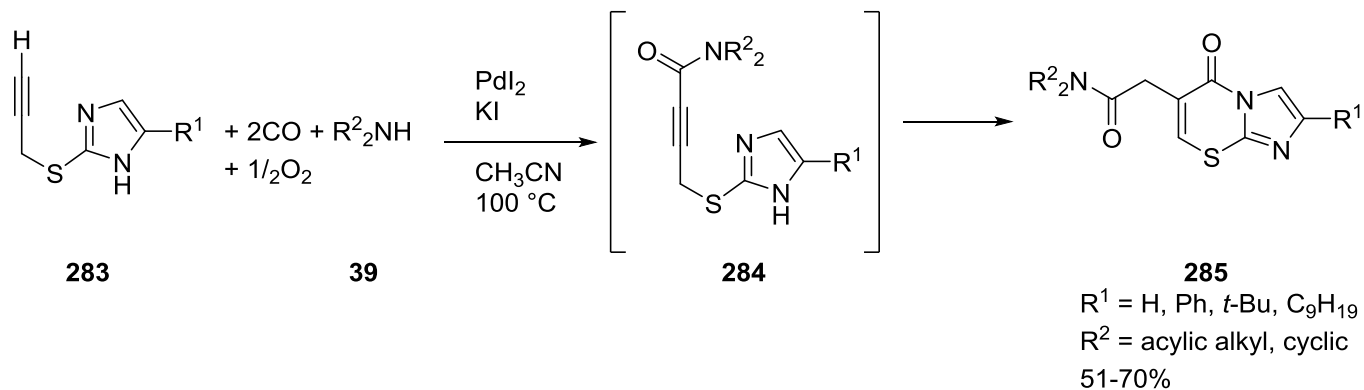
Scheme 86

Heating *b*-fused triazolo-5,6-dihydro-1,3-thiazin-4-ones **286** (see Scheme 118 for preparation of similar) to 200 °C with an aryl bromomethyl ketone **23** caused dehydrogenation to give the 1,3-thiazin-4-ones **287** (Scheme 87).[158] This is similar to the reactions in Schemes 7 and 18.
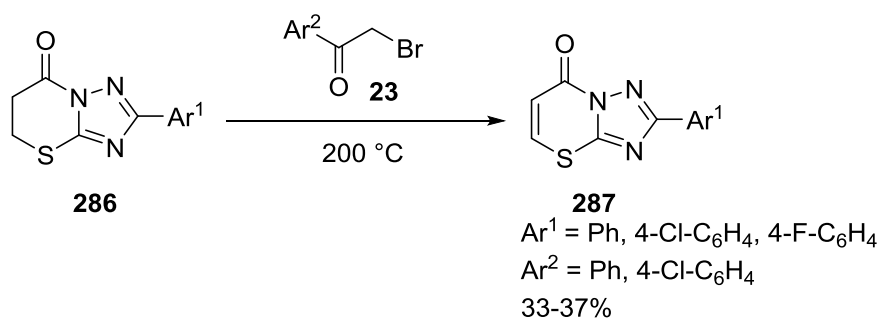
Scheme 87

2.4.6. *b*-Fused 2-imino or 2-amino derivatives of 1,3-benzothiazin-4-ones.   2,3,4,5-Tetrafluoro-1-benzoyl chloride **25** has been used in reactions with cyclic thioureas **288** and **52** to obtain benzimidazo- and imidazo-products, **289** and **290,** respectively (Scheme 88).[159]
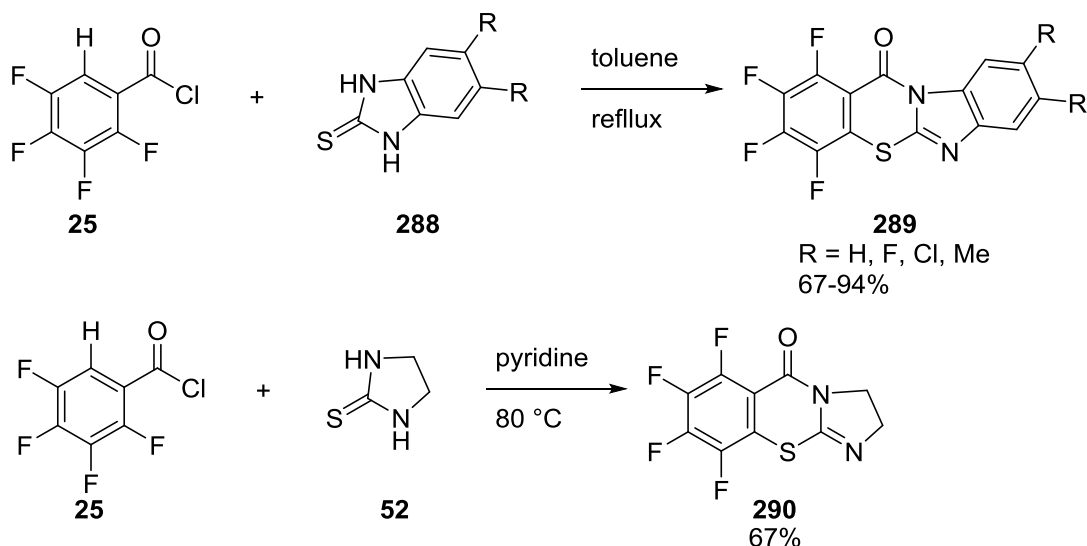
Scheme 88

Alternatively, 2-fluoro-1-benzoyl isothiocyanate **26** was reacted with cyclic thiourea **291** (Scheme 86). Evidently, the NCS moiety behaved as a leaving group in this case.[32]

26   **291**   **292**
                                                                              90%
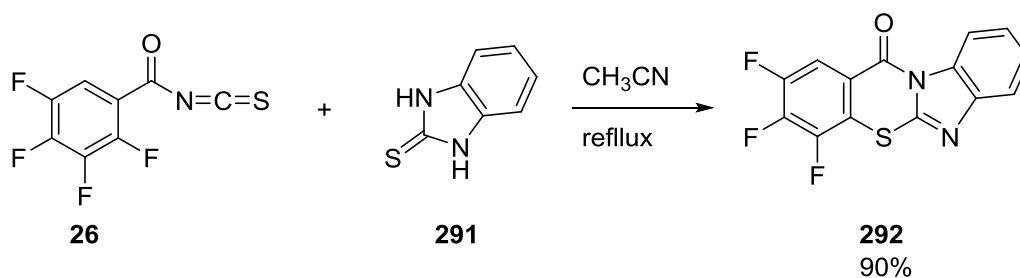
Scheme 89

b-Fused imidazolo- and benzimadazolo-1,3-benzothiazin-4-ones **296** and **298** were synthesized in a two-step process (Scheme 90). First, cyclic thioureas **294/291** were reacted with 2-iodobenzoyl chloride **293** in the presence of CuI/TBAB/Cs$_2$CO$_3$/DMF at 130 °C. This gave the sulfides **295/297**, which were cyclized by treatment with EDC.[160]

293   **294**   **295**   **296**
                                                                                                                      66%

293   **291**   **297**   **298**
                                                                                                                      65%
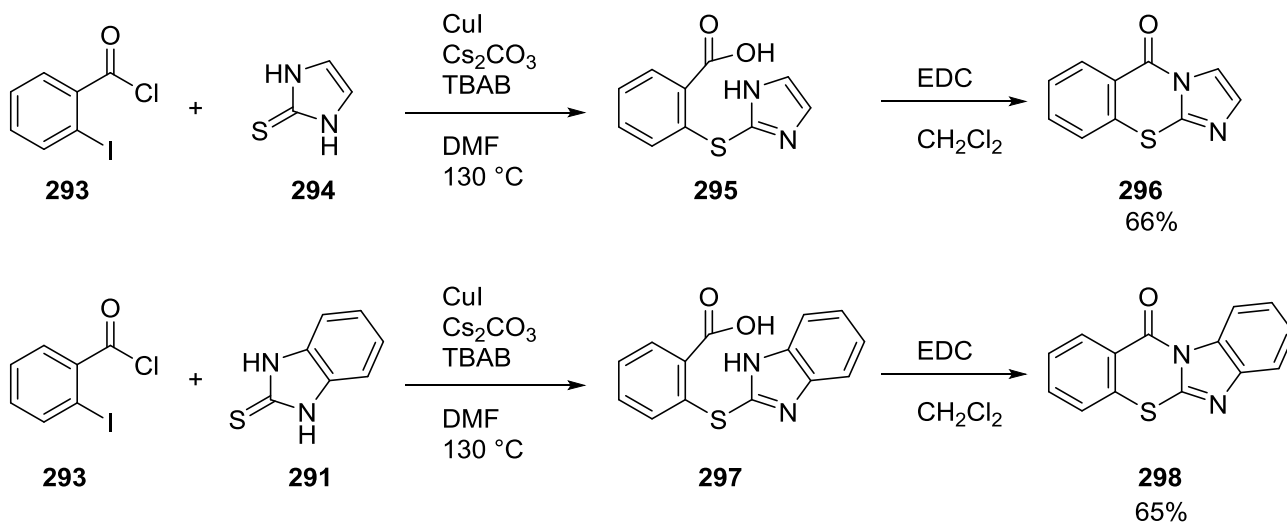
Scheme 90

In a similar reaction, 2-halo-1-benzoyl chlorides **299** were converted in a cascade reaction to the *b*-fused imidazole/benzimidazole products **301/302** (Scheme 91).[161] The halogen could be Cl, Br, or I. 1,10-Phenanthroline **300** was used as a ligand.
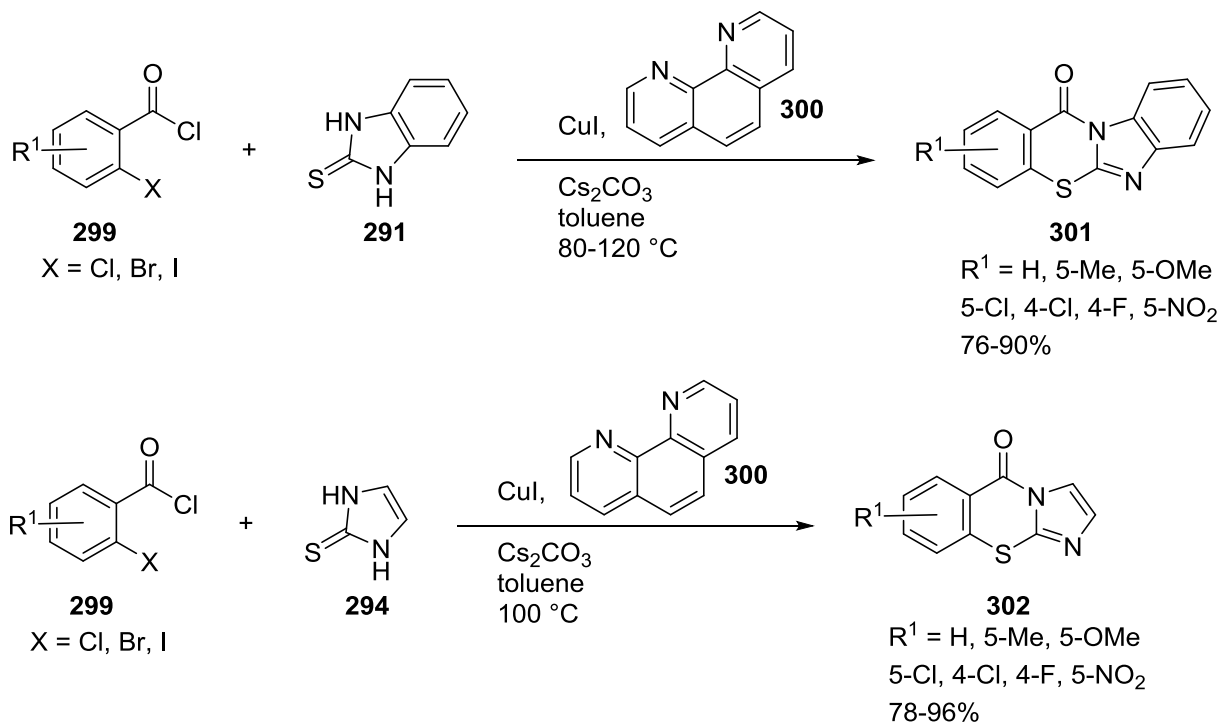
Scheme 91

Methyl 2-iodobenzoates **303** reacted with a wide range of cyclic thioureas **304** in a similar copper-catalyzed cyclization to give 5, 6, and 7-membered *b*-fused rings **305** (Scheme 92).[162]
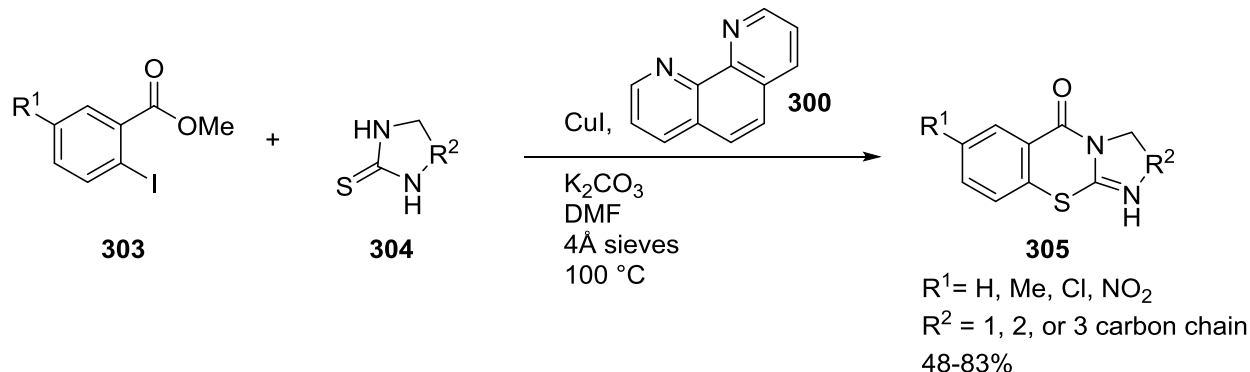
Scheme 92

Under similar conditions, 2-iodobenzoic acid **306** was coupled with cyclic thioureas **307** (Scheme 93).[163]
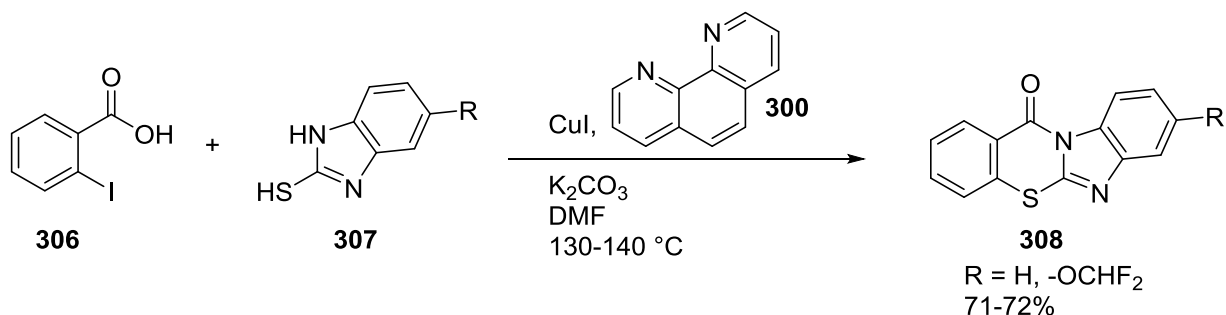
Scheme 93

The same type of reaction, but catalyzed by FeCl$_3$, has been used to prepare *b*-fused benzimidazole, imidazole, and triazole compounds **301/311** (Scheme 94).[164]
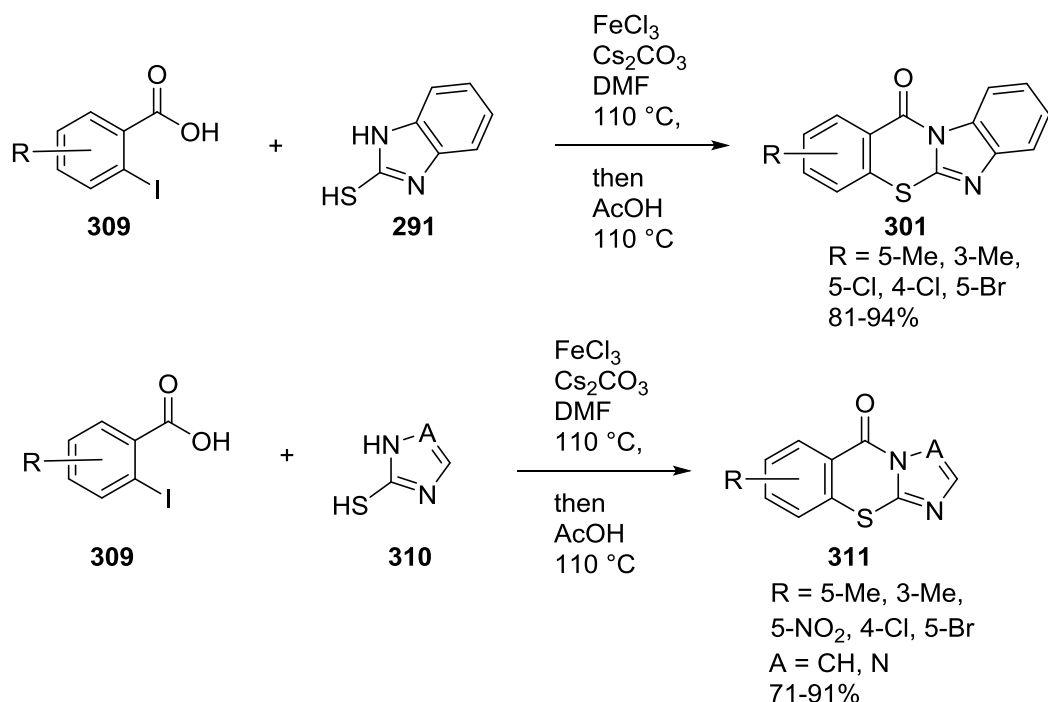
Scheme 94

Copper acetate has been used to promote the reaction of cyclic thioureas **291/314** with benzamides **312/315** to give the benzimidazole and imidazole compounds **301/315** (Scheme 95). The reaction was proposed to involve coordination of the sulfur, then bidentate coordination of the imidazole, oxidation from Cu(II) to Cu(III) by Cu(OAc)$_2$, insertion of Cu into the Ar-H bond, reductive elimination and finally ring closure by nucleophilic acyl substitution (Scheme 96).[165]
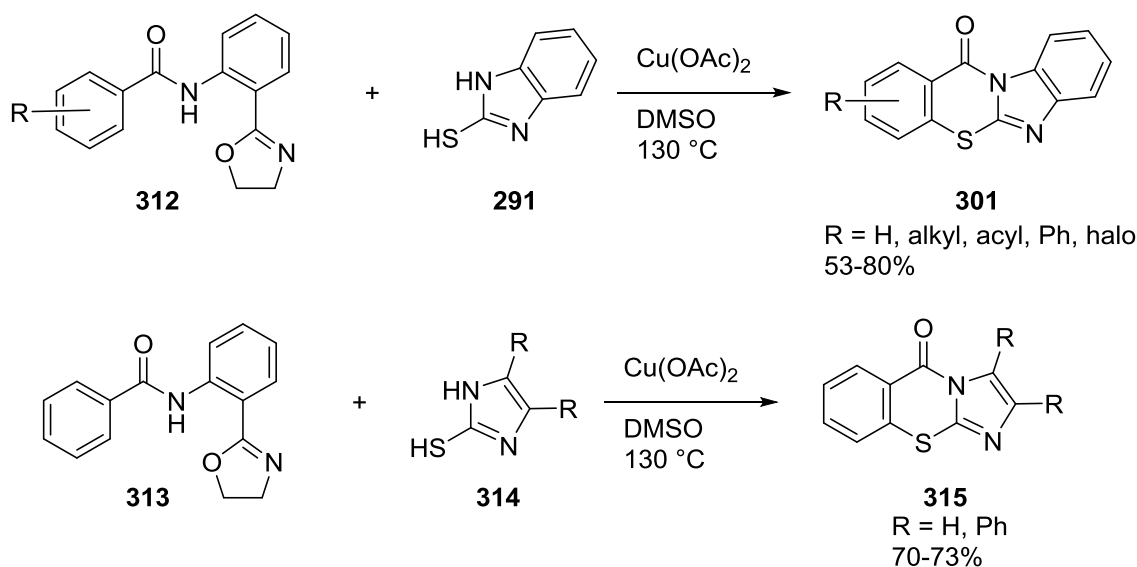
Scheme 95
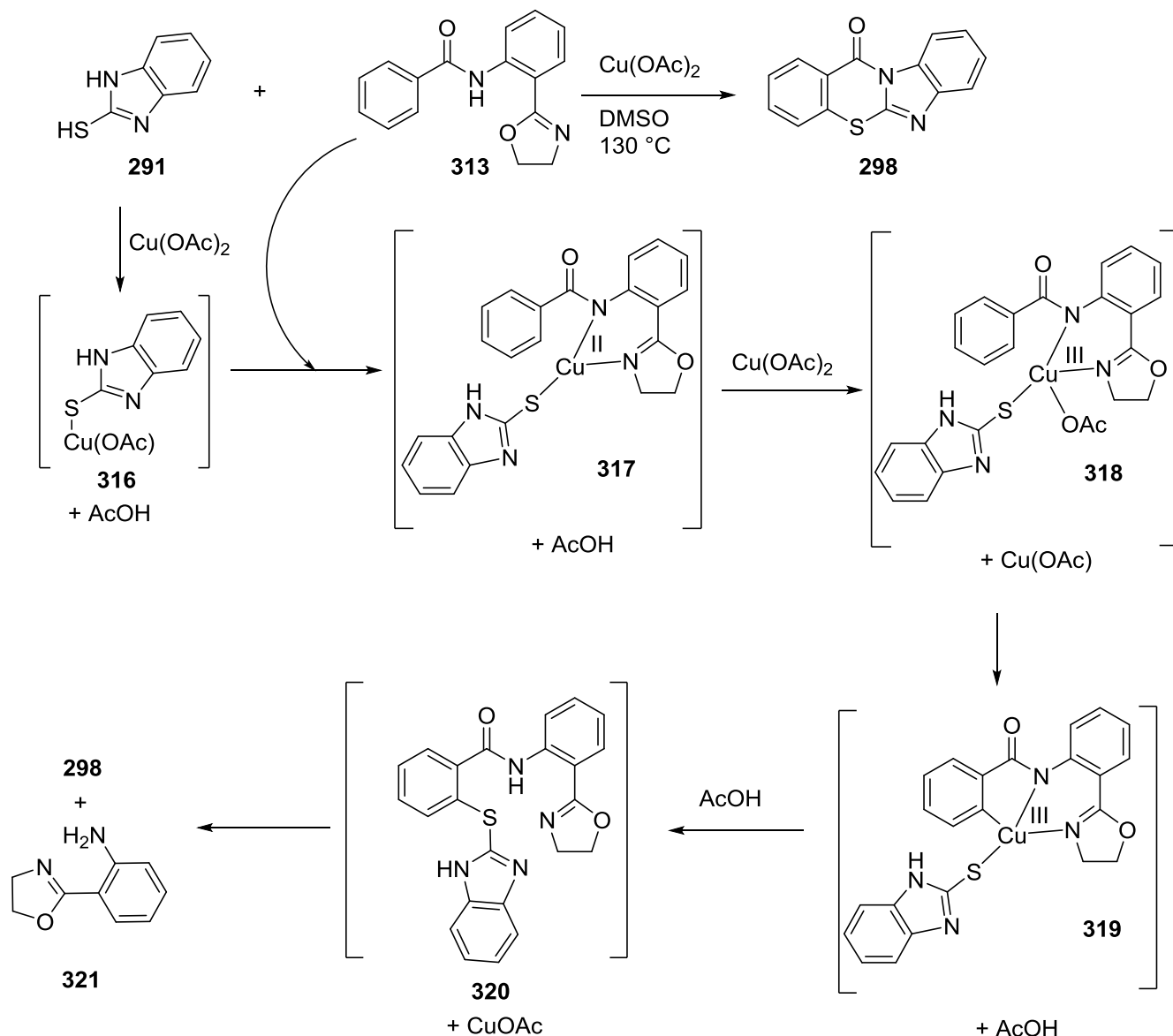
Scheme 96

2.4.7. *b*-Fused 2,3-dihydro-1,3-benzothiazin-4-ones with an exocyclic C=C. 2-Sulfanylbenzoic acids **147** have been reacted with imines generated *in situ* by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group, as in Scheme 107. When **322** was used, however, the unexpected product **323** was formed, in which an elimination had occurred to give an exocyclic C=C at C2 (Scheme 97).[166] The reaction may go through a different mechanism altogether than what is shown in Scheme 107.[166]

322

147

323
R = H, Me
41-42%
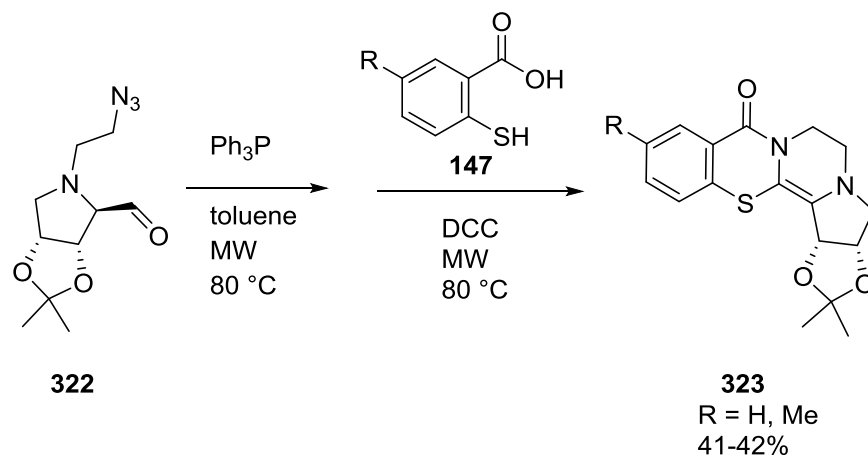
Scheme 97

Hydrolysis of 4-imino compound **324** gave the 4-oxo-triazole compound **325** (Scheme 98).[167]

324　　　　　　　　　　　　　**325**
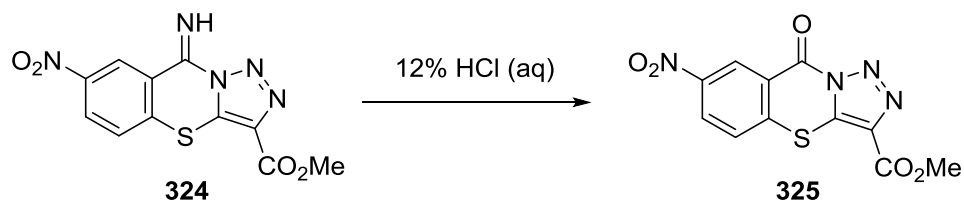
Scheme 98

Thermal sulfoxide electrophilic sulfenylation of indole **326** was used to obtain 1,3-benzothiazin-4-one **327** (Scheme 99).[168] The likely pathway[169] involved *in situ* formation of the sulfonium ion **328**.

326　　　　　　　　　　　　　**327**
　　　　　　　　　　　　　　　　19%

328
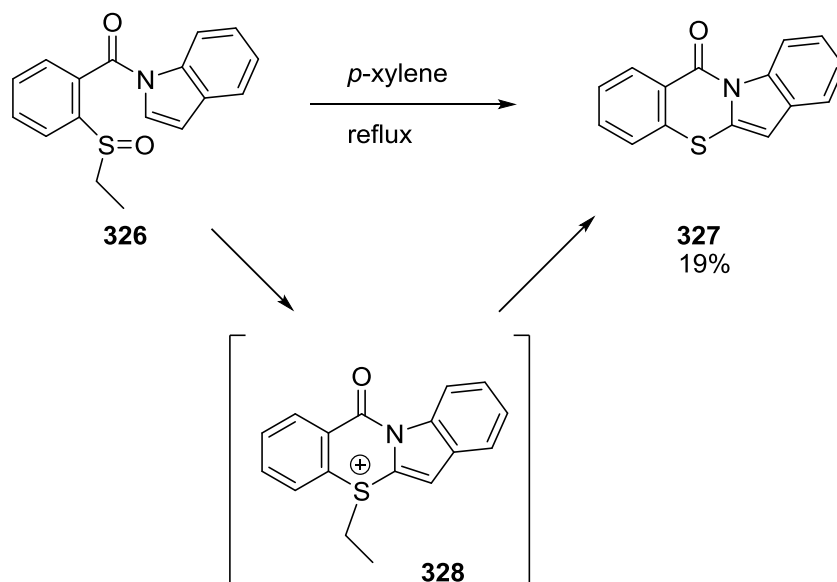
Scheme 99

Intramolecular cyclization of dimethyl indole-2,3-*bis*-(2-sulfanylbenzoate) **329** provided indole-fused 1,3-benzothiazin-4-one **330** (Scheme 100). This was carried out neat at 200 °C.[170] A similar reaction is shown in Scheme 125.

329

330
19%
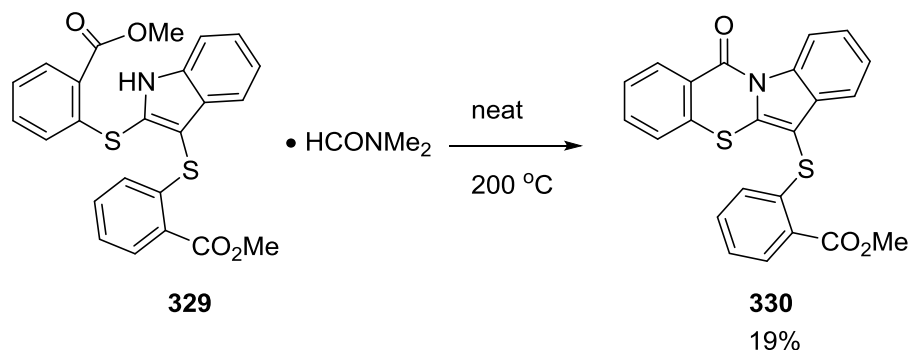
Scheme 100

The reaction of 2 equivalents methyl 2-sulfanylbenzoate **163** with 1 equivalent 1,1,2,2-tetracyanoethane **331** under basic conditions gave the tricyclic *b*-fused-pyrrolo product **334** (Scheme 101). The authors expected the reaction to stop at compound **332** but instead two consecutive cyclizations followed.[171]

163   **331**   **332**

334
36%

333   **163**
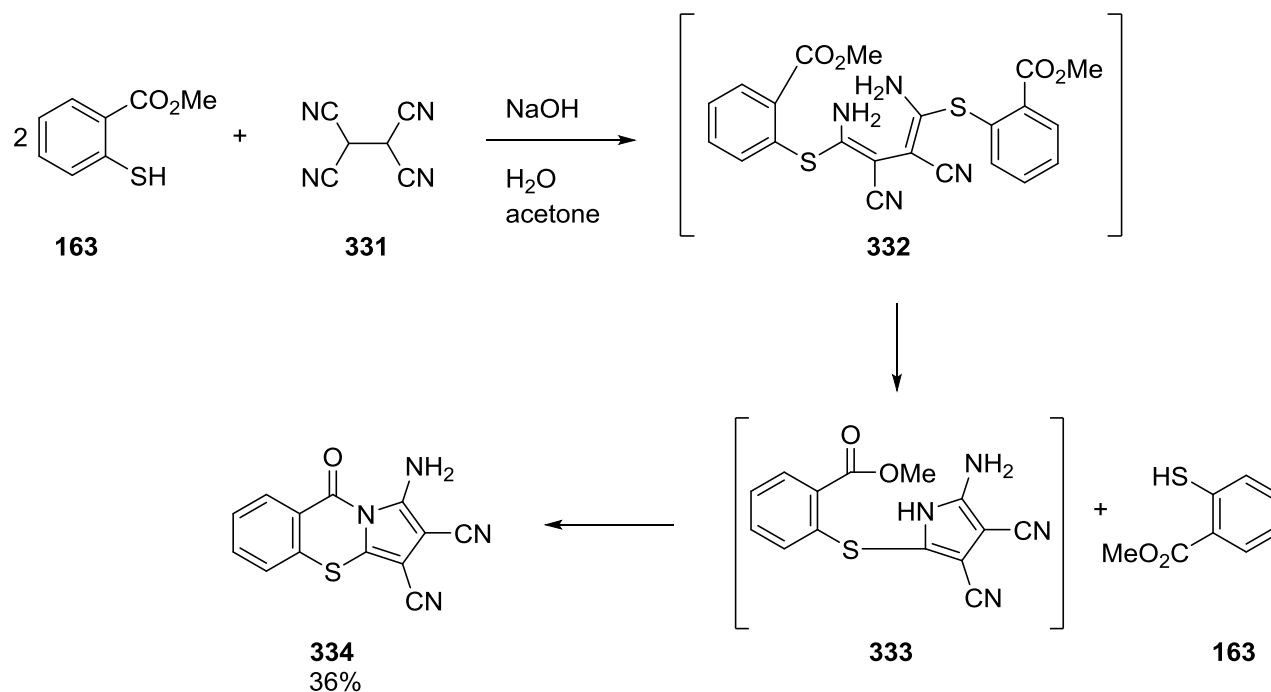
Scheme 101

In an intentional double cyclization reaction, *gem*-dibromovinyl compound **335** was treated with catalytic Cu₂O, 1,2-dimethylethanediamine (DMEDA) as the ligand, and K₂CO₃ in toluene at 70 °C. The tetracyclic *b*-fused indolo product **327** was obtained (Scheme 102). A proposed mechanism involved bidentate coordination to copper, insertion into a vinyl C-Br bond, elimination of HBr to give a cyclic copper intermediate

and then elimination of Cu to give *N*-vinylation. The process then essentially repeated itself, ending in *S*-vinylation.[172]
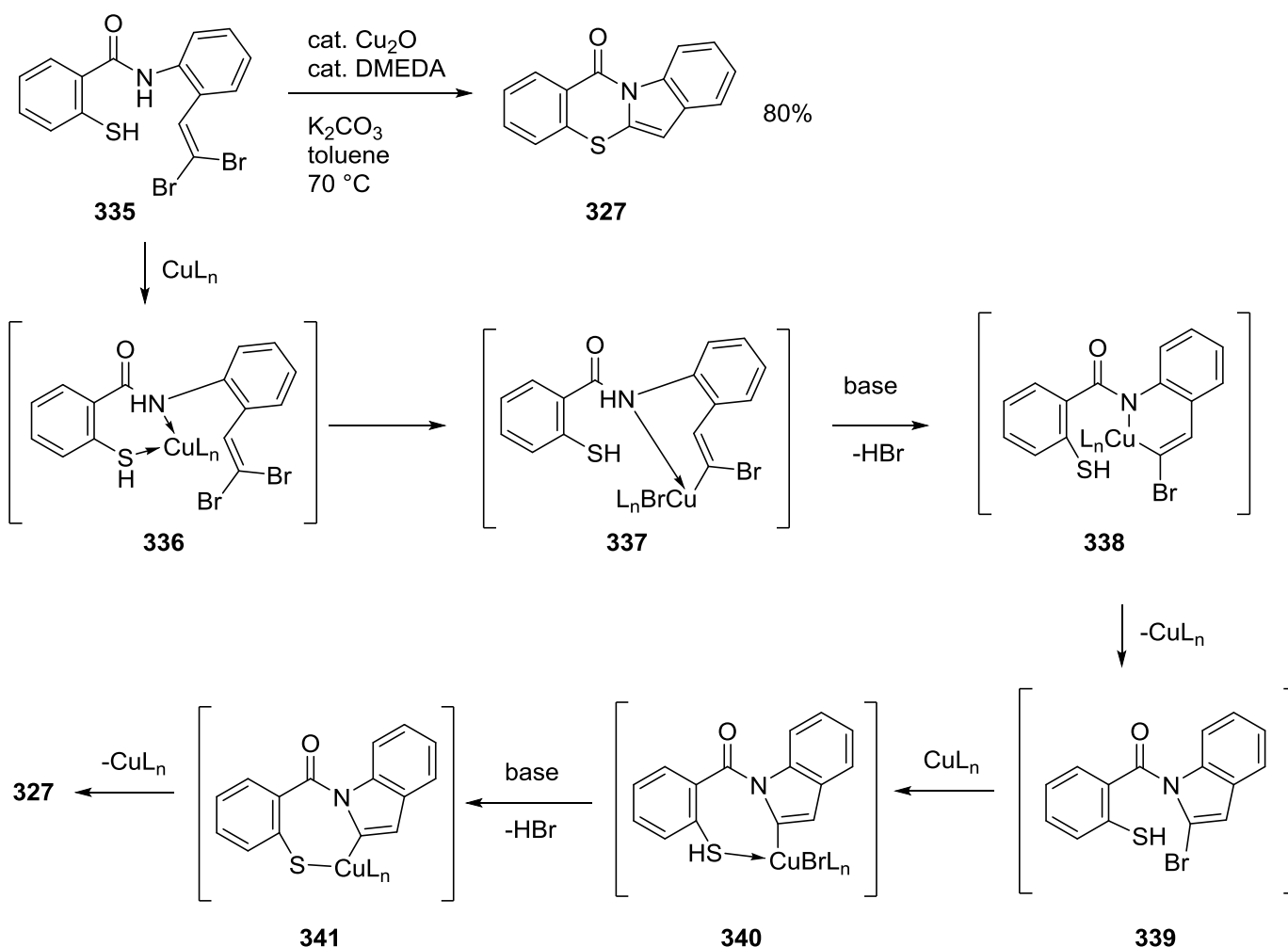
Scheme 102

2.4.8. *b*-Fused 2,3-dihydro-1,3-benzothiazin-4-ones. A three-component reaction of 5-nitro-2-fluorobenzoyl chloride **342**, NaSH, and five- or six-membered cyclic imines **343** containing another heteroatom (O or S) in the ring gave a number of *b*-fused 2,3-dihydro-1,3-benzothiazin-4-ones **344** (Scheme 103).[173]
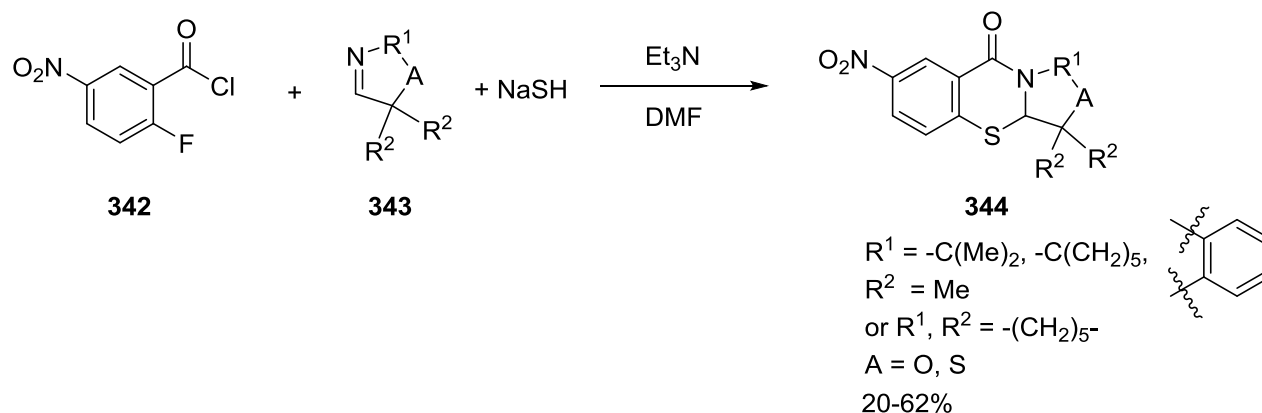
Scheme 103

Thionyl chloride has been used to generate the acid chloride. The acid chlorides **345** were prepared and used crude with imine **346** to give the pentacyclic products **347** (Scheme 104).[5]

R[1] = H, F, Cl, Br, OMe
R[2] = H, OMe
36% over two steps for
R[1] = R[2] = H
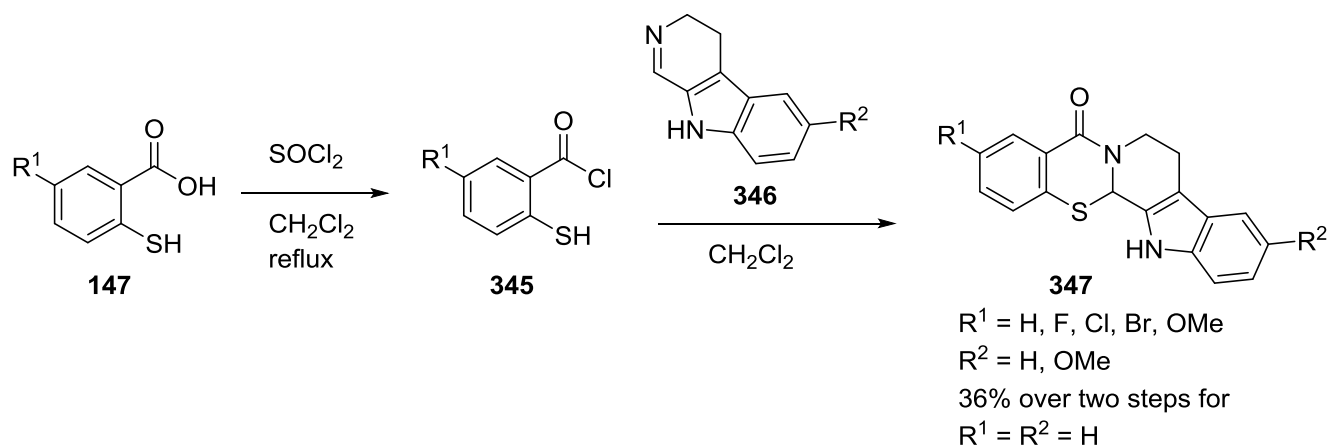
Scheme 104

b-Fused oxazolo-2,3-dihydro-1,3-benzothiazin-4-ones **349** were prepared by heating 2,5-dihydroxazoles **348** with 2-sulfanylbenzoic acid **47** in toluene (Scheme 105).[174]

R[1] = Me, Ph
R[2] = alkyl
R[3] = H, Me
or R_2/R_3 = -(CH$_2$)$_5$-
27-74%
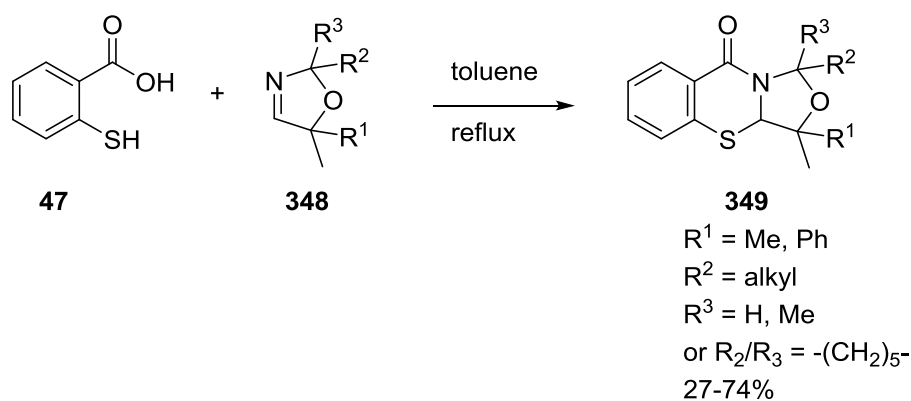
Scheme 105

T3P **159** has also been used to prepare a variety of *b*-fused 1,3-benzothiazin-4-ones **351** (Scheme 106).[106,107]

R[1] = H, Me
31-99%
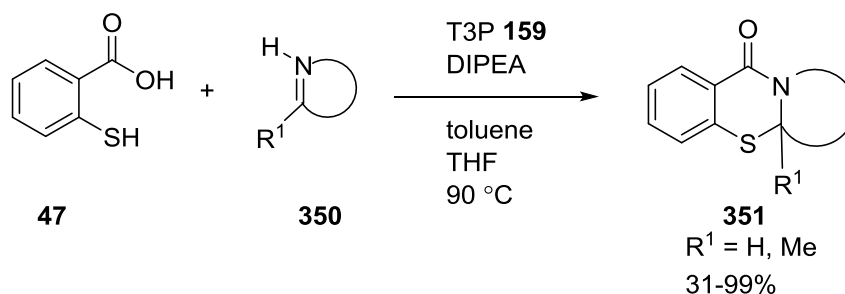
Scheme 106

2-Sulfanylbenzoic acid **47** has also been reacted with imines generated *in situ* by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group (**352**).[9,175,176] The three reactions were performed in one pot with microwave irradiation of the toluene solution at 100 °C (an example[175] is shown in Scheme 107). The sequence was presumed to begin with reaction of triphenylphosphine with the azide functional group of the sugar **355** to give iminophosphorane **353**. The aldehyde form **354** of the sugar then underwent an intramolecular aza-Wittig reaction to give the cyclic imine **355**. 2-sulfanylbenzoic acid **47** was then added and microwaved again to form *b*-carbohydrate-fused 2,3-benzothiazin-4-one **356**. In other examples, the carboxylic acid activator DCC was also added in the last step.[9,175] Similar reactions are in Schemes 108, 131, and 140.
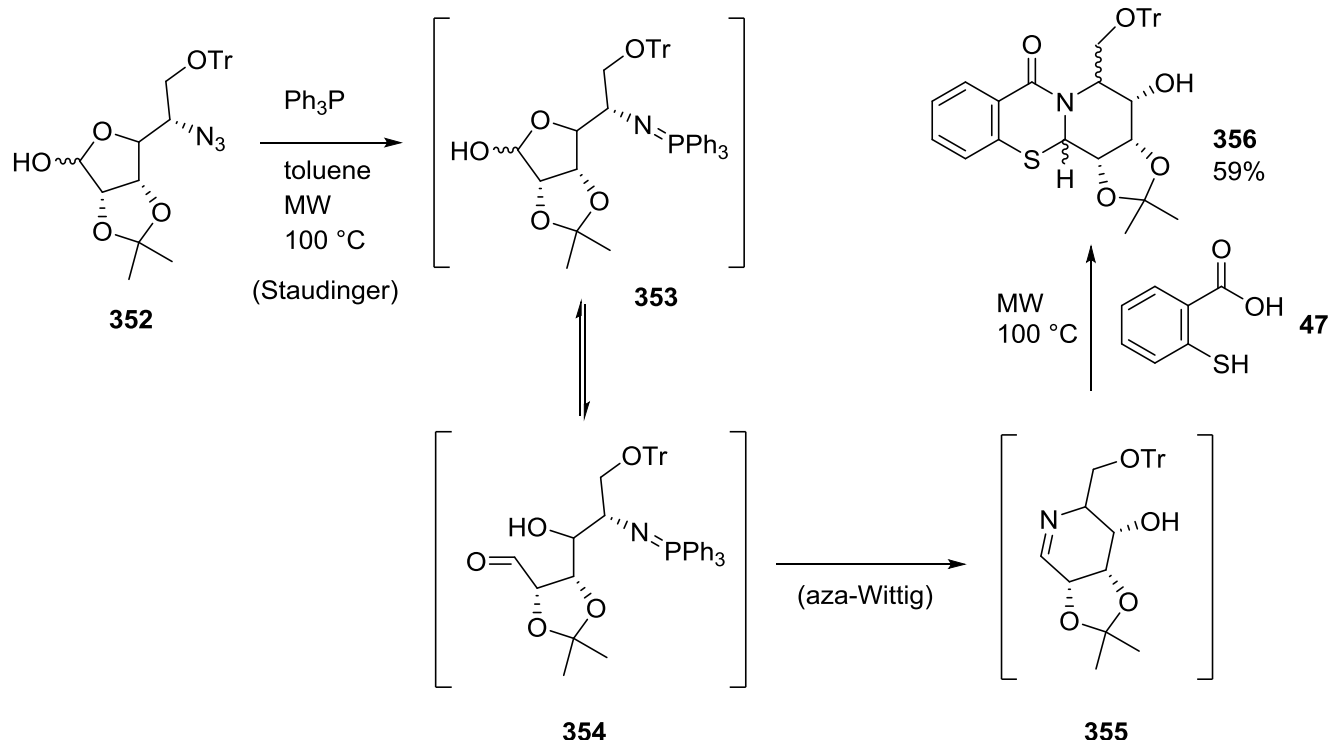
Scheme 107

When pyrrolidine azide **357** was used, the products were **359**. The three reactions were done in one pot with microwave irradiation of the toluene solution at 80 °C (Scheme 108) to give **358**. 2-Sulfanylbenzoic acids **147** and DCC were then added and irradiated with microwaves again to form **359**.[166] The reaction pathway was presumably the same as in Scheme 107. Similar examples can be found in Schemes 107, 131, and 140.

In a carbodiimide-promoted reaction with an unusual dearomatization of pyridine, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCl) **361** was used to form pentacyclic structure **362** (Scheme 109). The pathway proposed was activation of the carboxylic acid by EDCl **361**, then attack by the pyridine nitrogen to give the iminium ion intermediate **364**. Attack by sulfur gave the heterocycle **362** with loss of the aromaticity of the pyridine ring.[177]
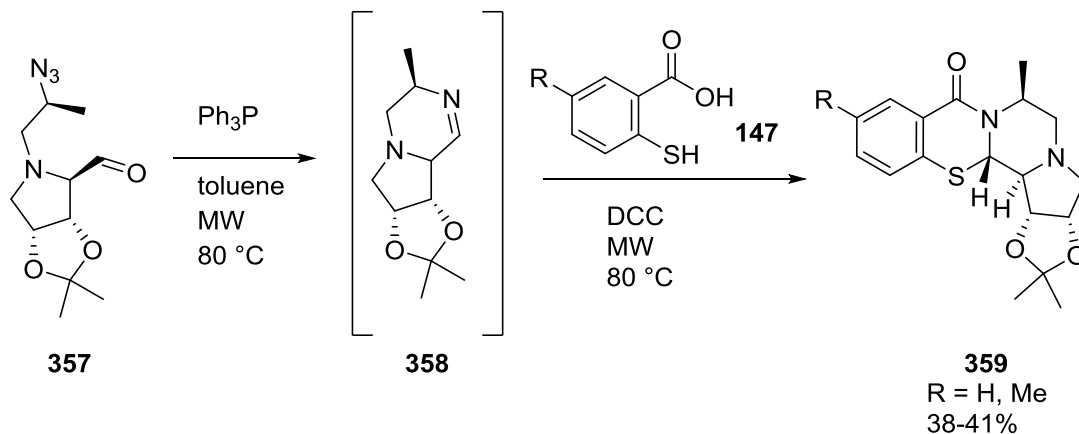
Scheme 108
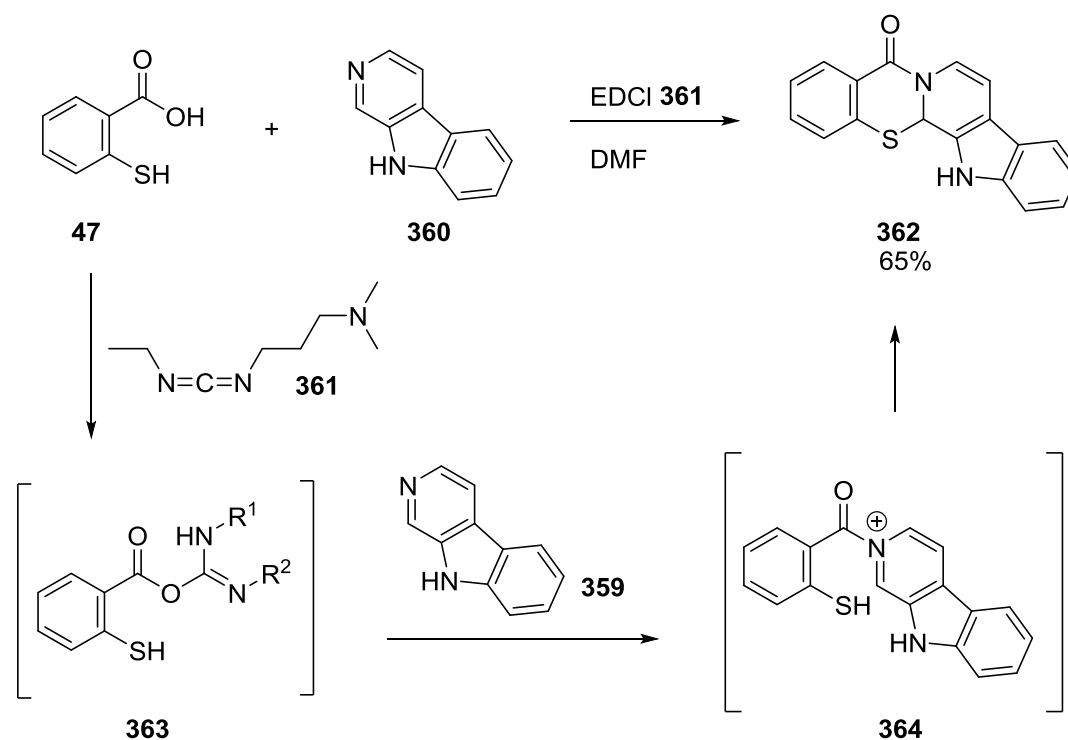
Scheme 109

A novel method recently reported used 2-iodobenzamides **365** and potassium sulfide to construct tetracyclic systems **366** (Scheme 110).[178] The reaction was catalyzed by copper(II) acetate with tetramethylene-diamine (TMEDA) as ligand and run in *N*-methylpyrrolidone (NMP) at 120 °C. The reaction performed better in air than in oxygen or nitrogen atmosphere. The proposed pathway was copper-catalyzed coupling of the sulfide, followed by single-electron transfer redox step to give iminium ion **368**, and then finally nucleophilic attack by sulfur to close the ring.
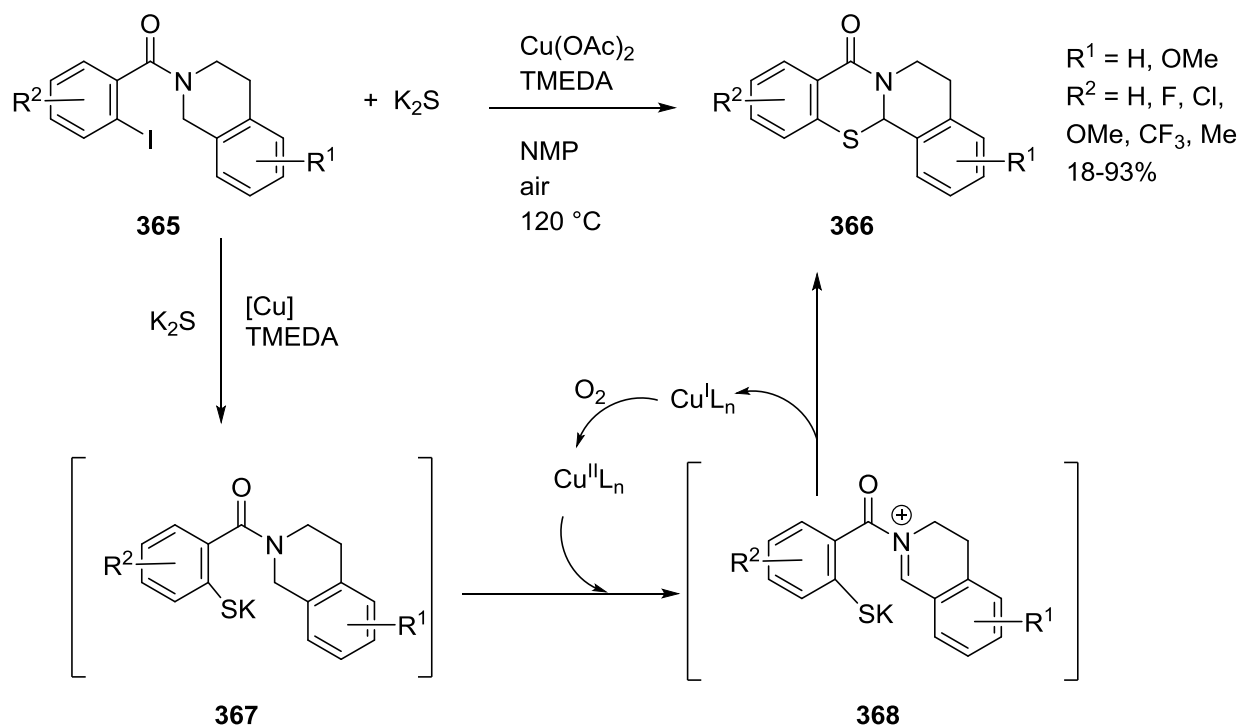
Scheme 110

2.4.9. *b*-Fused 2-imino or 2-amino derivatives of 5,6-dihydro-1,3-thiazin-4-ones. A common strategy for *b*-fused heterocycles **371** has been condensation of a cyclic thiourea **370** with a 3-halopropionic acid **369**, where the halide is bromine[179-200] or chlorine[201-205] (Scheme 111). In one case, instead of NaOAc/Ac$_2$O/AcOH/reflux (52%), ionic liquid *N*-methylpyridinium tosylate was used at 100-110 °C (68%).[205] The bromide has also been used with NaOEt/KI/DMF/reflux followed by Ac$_2$O/pyridine.[206]
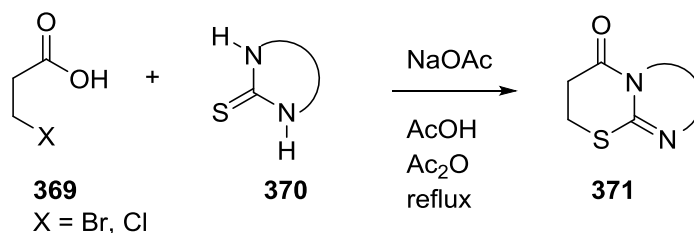
Scheme 111

Similarly, 3-chloropropanoyl chloride **95** with potassium carbonate, acetonitrile, and phase transfer catalyst tetrabutyl ammonium bromide (TBAB) was reacted with a cyclic thiourea **372** at room temperature to give benzimidazole **373** (Scheme 112).[207] 3-Bromopropanoyl chloride **374** with K$_2$CO$_3$ in DMF at 120 °C has similarly been used to yield pyrimidines **376** (Scheme 113).[208]
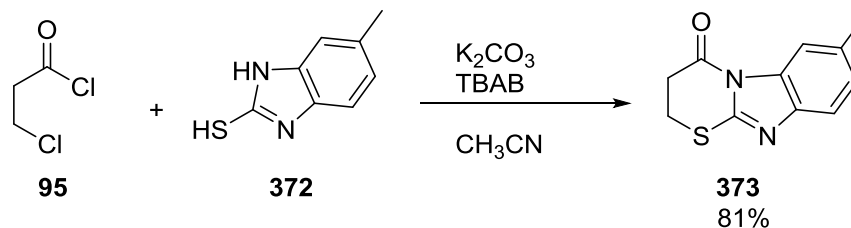
Scheme 112
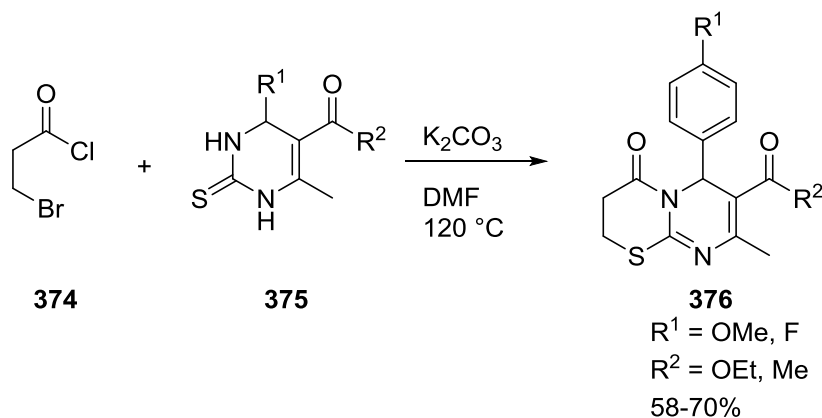
Scheme 113

Reaction of cyclic thiourea **378** with malonic acid **377** and acetyl chloride **379** in DMF gave the 6-oxo-*b*-fused compound **380** by condensation of both malonic acid groups (Scheme 114).[209] There was a C=O at C6 of **380**. The paper does not comment on the reaction.
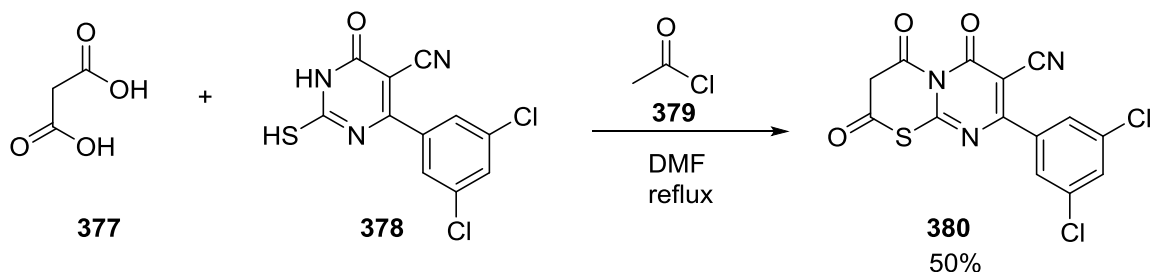
Scheme 114

Malonyl dichloride **16** was used in a similar fashion (Scheme 115).[210]
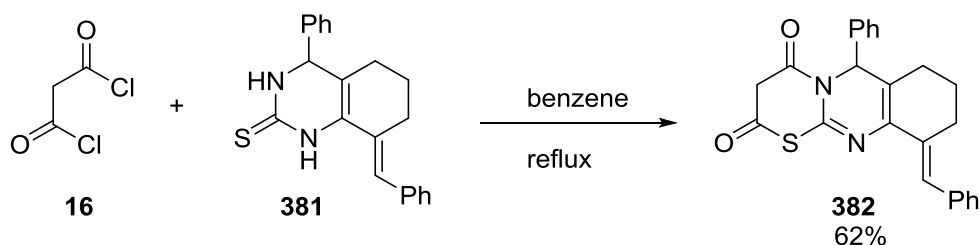
Scheme 115

Triazole **383** was cyclized by treatment with acetic anhydride and pyridine (Scheme 116).[211]

383

384
62%
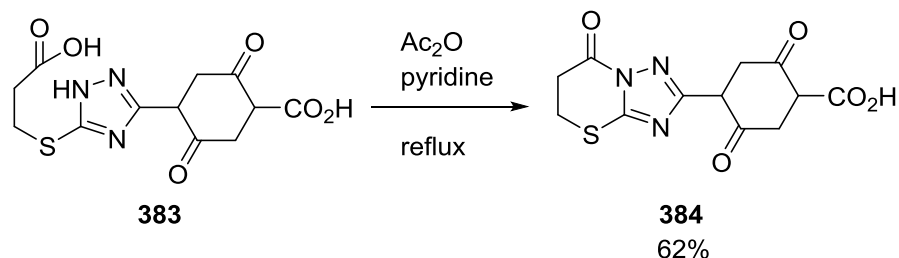
Scheme 116

Cyclic thiourea **385** has been reacted with 3-aryl-2-propenoyl chlorides **131** to give fused pyrimidine HCl salts **386** by conjugate addition, using refluxing pyridine/benzene (Scheme 117).[212]

131   **385**

386
Ar = Ph, 4-OMe-
C$_6$H$_4$, 3-NO$_2$-C$_6$H$_4$
58-72%
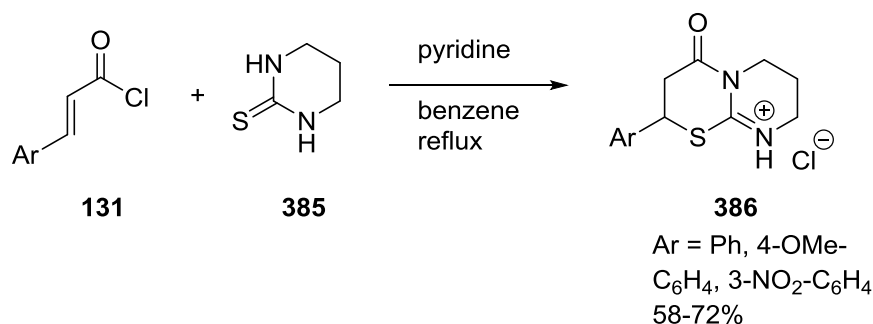
Scheme 117

A similar method delivered fused 1,2,4-triazoles **387** as the free bases (Scheme 118).[213,214] Reactions in acetone (Ar = H, R = Ph, 4-OMe-C$_6$H$_4$, 4-F-C$_6$H$_4$) produced the HCl salts (60-71%).[215]

131   **281**

387
Ar = Ph, 3,4-(OMe)$_2$-C$_6$H$_3$, 4-NO$_2$-
C$_6$H$_4$, 4-Cl-C$_6$H$_4$,4-F-C$_6$H$_4$, 1-napthyl,
2-thienyl, 3,4-methylenedioxyphenyl
R = H, Ph, 4-NO$_2$-C$_6$H$_4$, 4-OMe-C$_6$H$_4$
50-81%
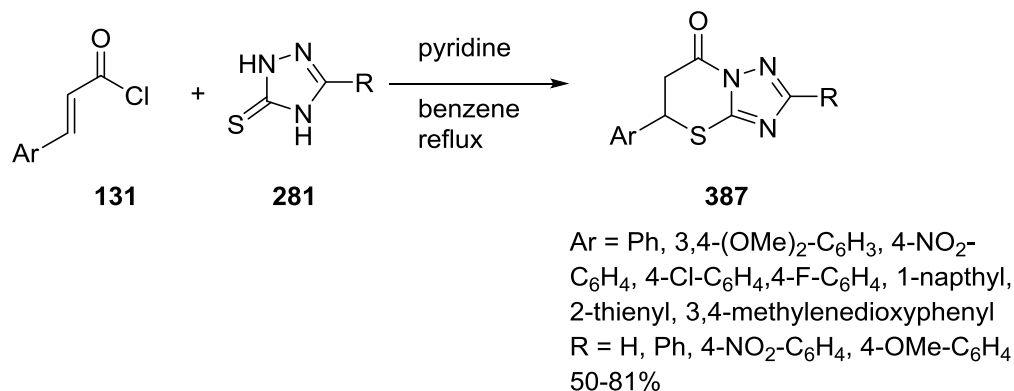
Scheme 118

Benzimidazole-2-thiones **307** and 3-aryl-2-propenoyl chlorides **131** were reacted with pyridine to give the *b*-fused benzimidazole compounds **388**. One benzimidazole was prepared using K$_2$CO$_3$/TBAB/acetonitrile

(48%).[207] However, imidazoline-2-thiones **52** in pyridine only gave *N*-acylated products. Fortunately, reaction in acetone gave the desired compounds **389** as the HCl salts (Scheme 119).[216]

R = H, OEt
Ar = Ph, 4-OMe-C$_6$H$_4$, 2-OMe-C$_6$H$_4$,
3,4-(OMe)$_2$-C$_6$H$_3$, 3,4,5-(OMe)$_3$-C$_6$H$_2$,
3-NO$_2$-C$_6$H$_4$, 4-F-C$_6$H$_4$, 2-thienyl, 2-
furyl, I 1-(3,4-methylenedioxy)phenyl
53-82%

Ar = Ph, 4-OMe-C$_6$H$_4$, 3-NO$_2$-C$_6$H$_4$,
2-thienyl
47-54%
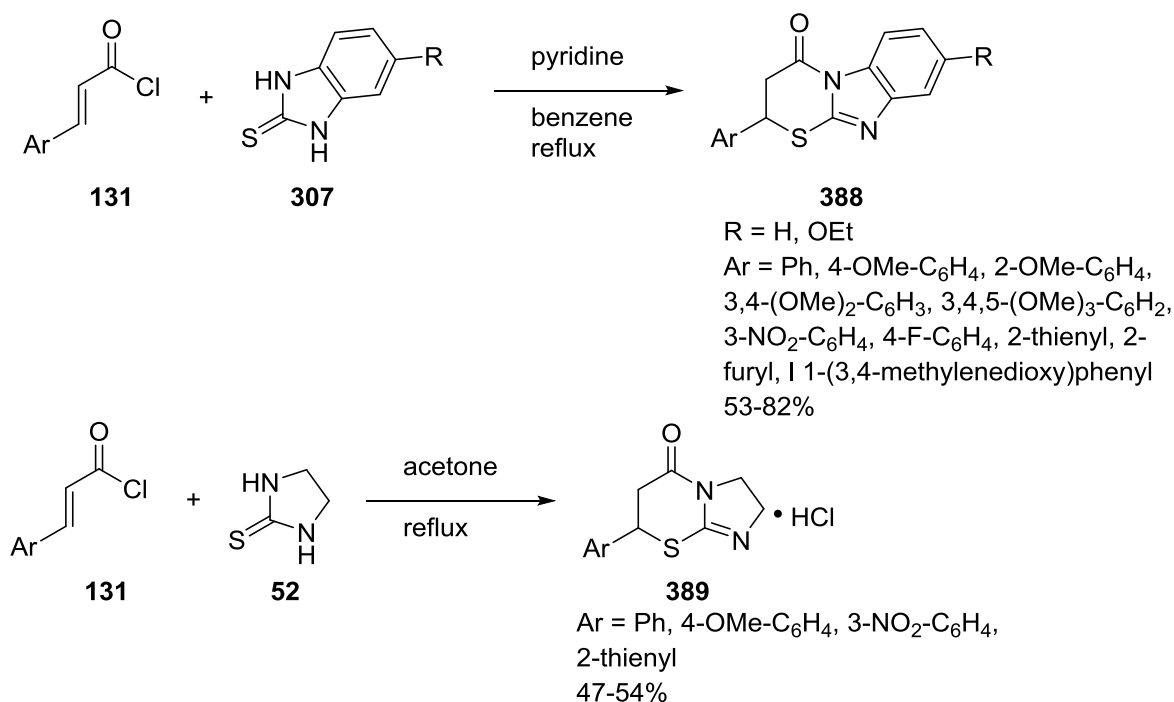
Scheme 119

Conjugate addition of sulfanyltriazoles **281** to 4-arylidene-5-oxazolones **390** gave *b*-fused triazolo-5,6-dihydro-5,6-substituted-1,3-thiazin-4-ones **391** (Scheme 120). Presumably, Michael addition gave intermediates **392**, and then nucleophilic attack by a nitrogen from the original thiourea led to products **391**.[217]

Ar^1 = 2-Cl-C$_6$H$_4$, 4-Cl-
C$_6$H$_4$, 2-OMe-C$_6$H$_4$
Ar^2 = Ph, 4-Me-C$_6$H$_4$, 4-
F-C$_6$H$_4$, 2-OMe-C$_6$H$_4$
60-71%
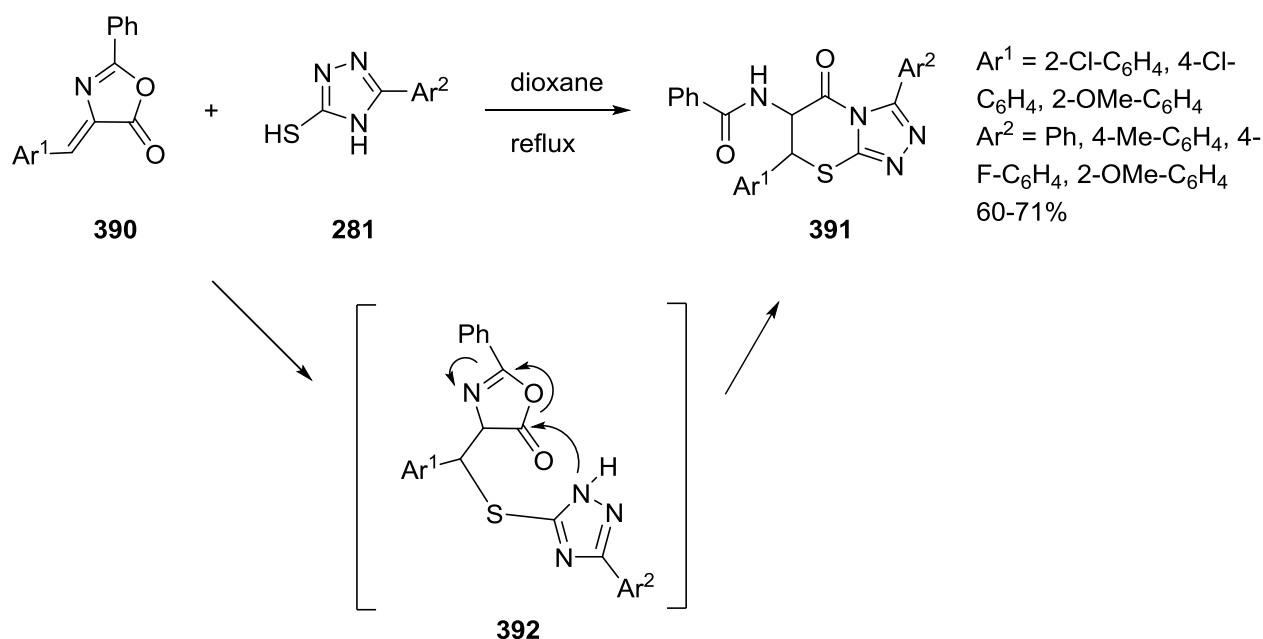
Scheme 120

Intramolecular conjugate addition of sulfanyltetrazole **393** gave *b*-fused tetrazole **394** (Scheme 121).[218]
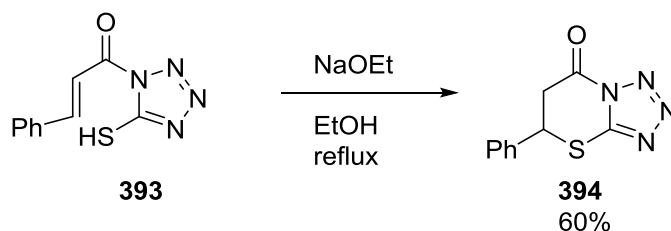
Scheme 121

In a stepwise approach, cyclic thiourea **395** was treated with KOH to give salt **396**. Reaction with 3-chloropropanoyl chloride **95** in refluxing ethanol then gave intermediate **397**. Cyclization to **398** was accomplished with catalytic KI in refluxing ethanol (Scheme 122).[219]
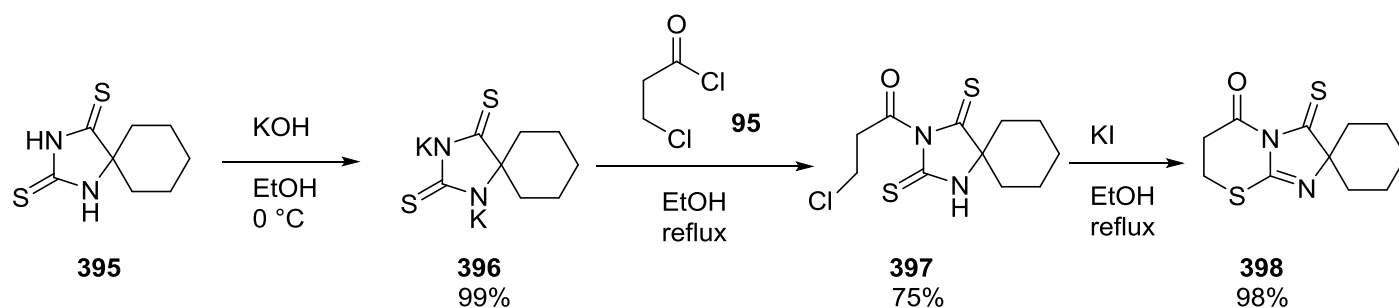
Scheme 122

When the thiolactams **399** used as in Scheme 126 had two methyl groups on the carbon α to the thione, elimination could not occur and the products were isolated as betaines **403** (Scheme 123).[220]
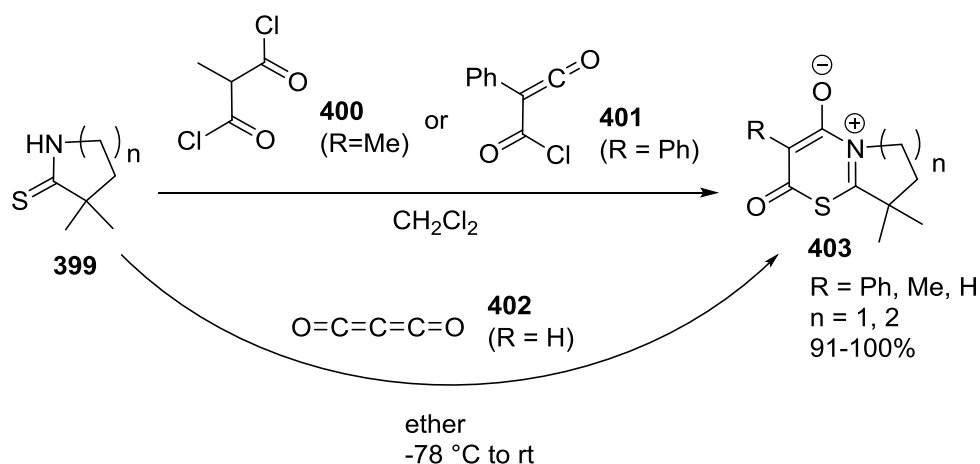
Scheme 123

2.4.10. *b*-Fused 2,3,5,6-tetrahydro-1,3-thiazin-4-ones with an exocyclic C=C. Sulfanyl imidazoles **404/407** were intramolecularly cyclized to **406/408** with solid-supported carbodiimide **405** in two different ways. One

method involved CH$_2$Cl$_2$/DMF at room temperature.[221] Alternatively, the reaction was performed with in the same solvents under microwave irradiation (Scheme 124).[222]

R^1 = H, Me, Et
R^2 = F, OMe, CF$_3$
61-90%

Ar = 4-F-C$_6$H$_4$, 4-OMe-C$_6$H$_4$,
4-CF$_3$-C$_6$H$_4$, Bu, 3,4-(OMe)$_2$-
C$_6$H$_4$, 4-AcHN-C$_6$H$_4$,2-thienyl
R = H, 4-Me, 4-Br
40-95% crude
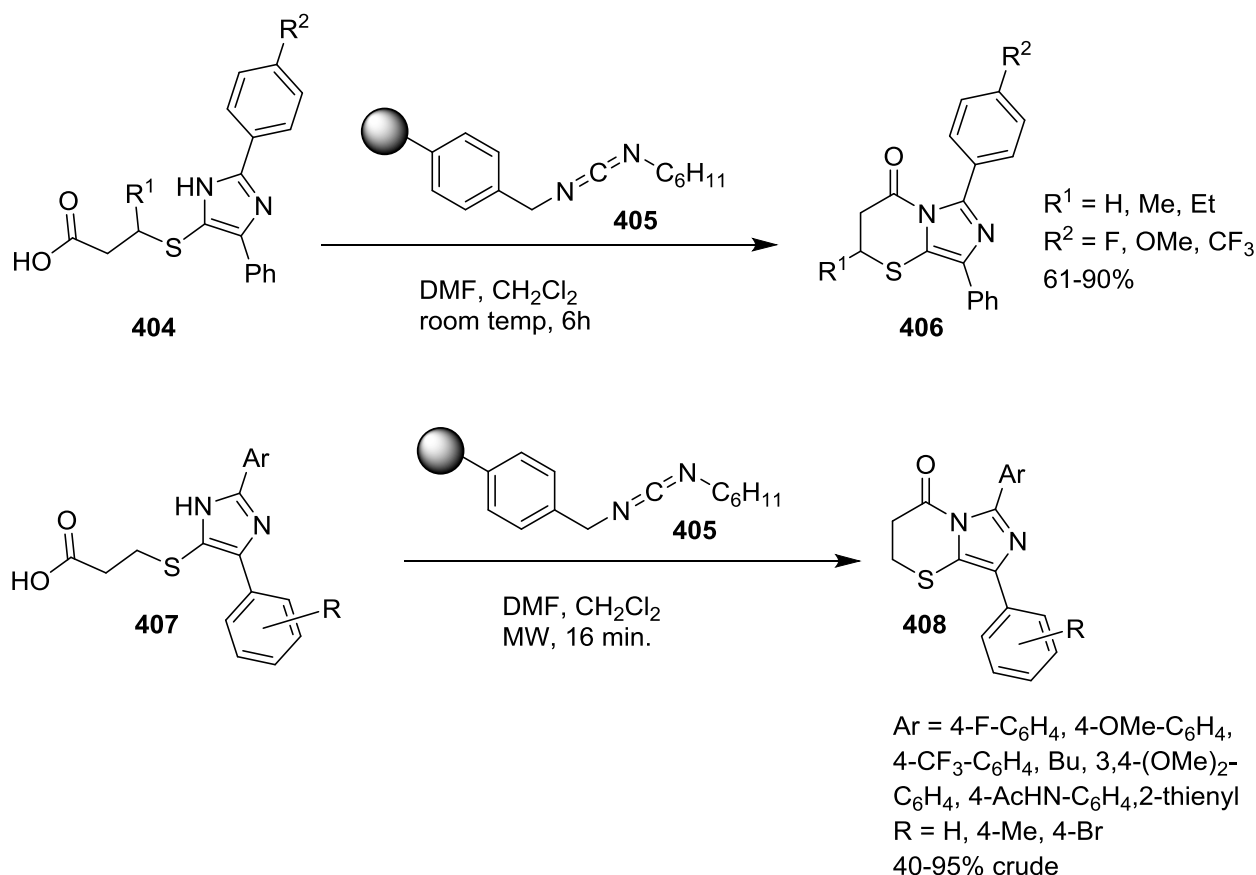
Scheme 124

Intramolecular cyclization of indole *bis*-(methyl thioalkanoate) **409** provided compound **410** (Scheme 125). This was done either neat at 185-190 °C, or in refluxing tetralin (206 °C)[223] and is similar to the reaction in Scheme 100.
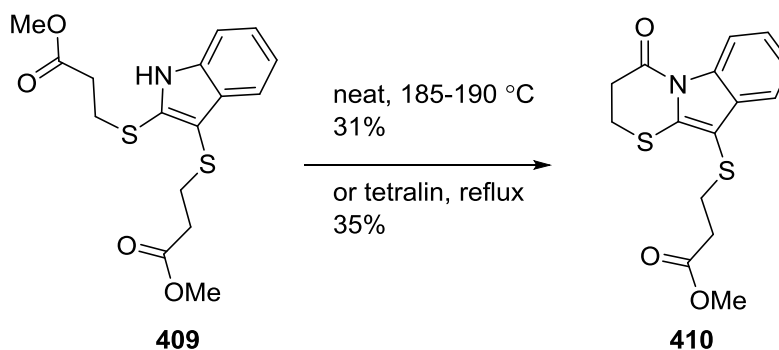
Scheme 125

Reaction of thiolactams **411** with either malonyl dichloride **16** or (chlorocarbonyl)phenyl ketene **401** gave *b*-fused compounds **412** with an exo C=C at C2 and a carbonyl at C6. This same transformation also occurred with carbon suboxide (C_3O_2) (Scheme 126).[224]
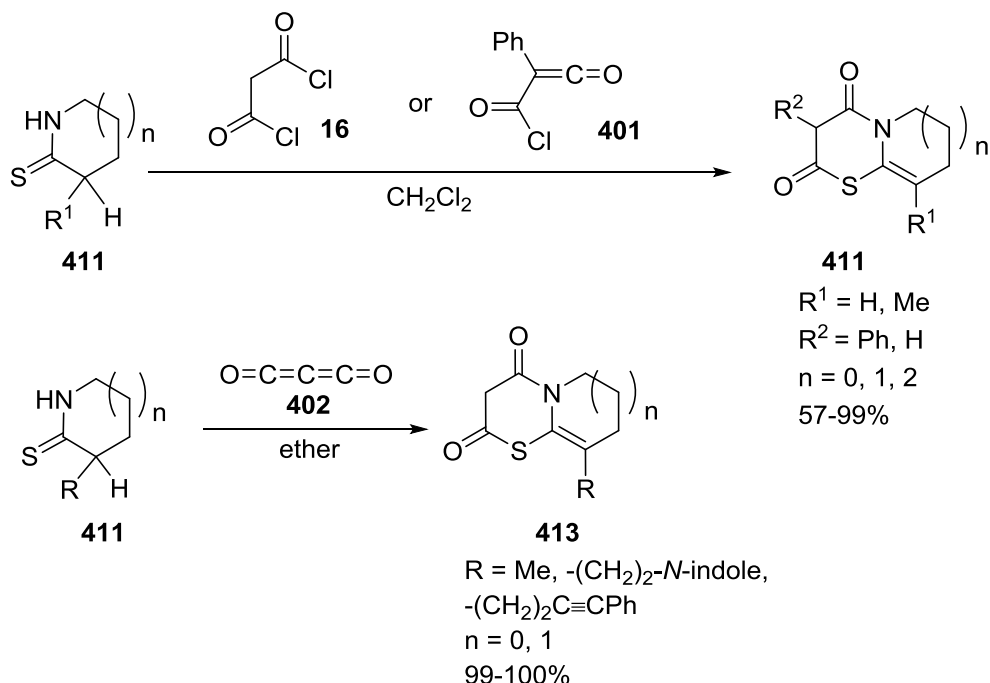
Scheme 126

Thiolactams **414** were reacted with 3-aryl-2-propenoyl chlorides **131** in the presence of pyridine to yield compounds **415** *via* conjugate addition (Scheme 127).[225]
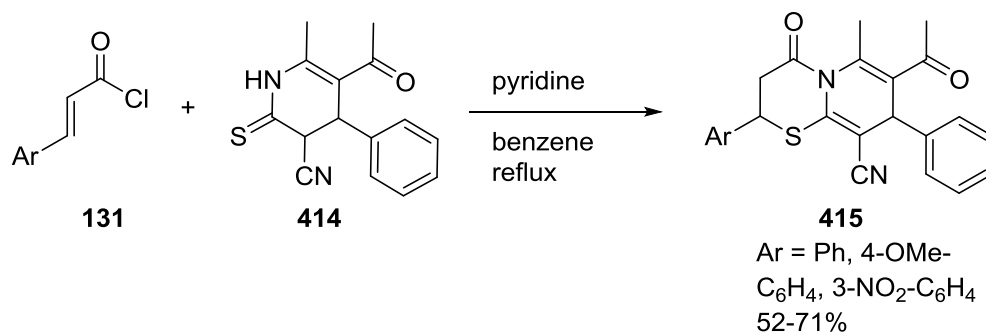
Scheme 127

2.4.11. *b*-Fused 2,3,5,6-tetrahydro-1,3-thiazin-4-ones. An intramolecular cyclization of an aldehyde[226] or its dimethyl acetal **416**[227] was achieved by treatment with trifluoroacetic acid (TFA), which both deprotected the sulfur and catalyzed the cyclization. The reaction was diastereoselective. The authors posited that the amido nitrogen attacked the aldehyde to give a cyclic iminium ion **417**, and then a second cyclization occurred by attack of the sulfur, which occurred in a diastereoselective fashion to give **418** (Scheme 128).[227]
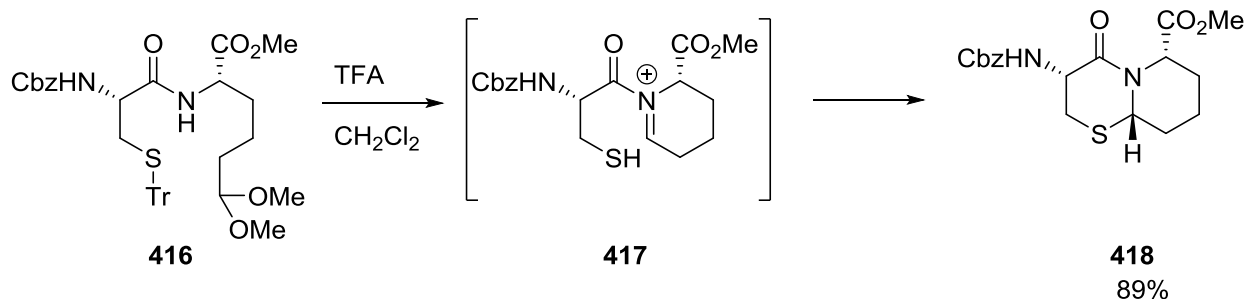
Scheme 128

In chemistry similar to Scheme 128, treatment of compounds **419** with TFA, thioanisole, and water (90:5:5) gave cyclized compounds **420** (Scheme 129).[7,228,229] The same reaction had earlier been used to make peptide-heterocycle hybrids.[230,231]
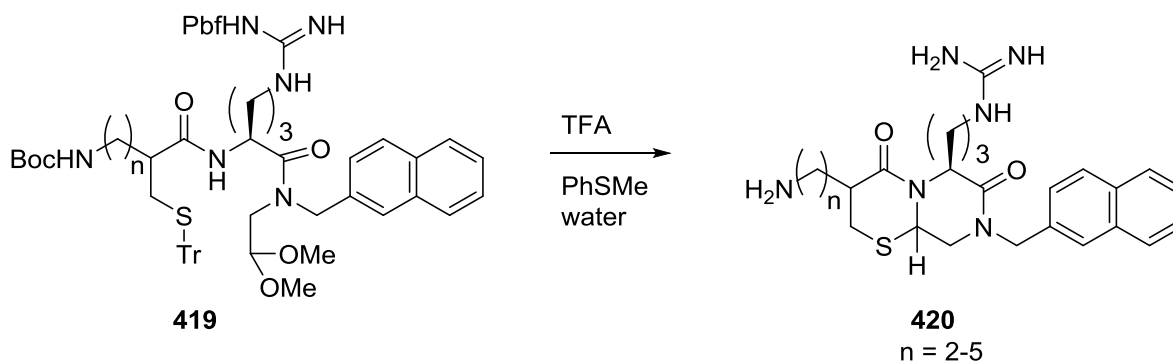
Scheme 129

T3P **159** in DIPEA has been used to prepare *b*-fused compounds **422** starting from either 3-sulfanylpropanoic acid (**190**) or from *N*-acetylcysteine (**187**, R = NHAc) (Scheme 130). Another example used a ketimine instead of **421**.[133]
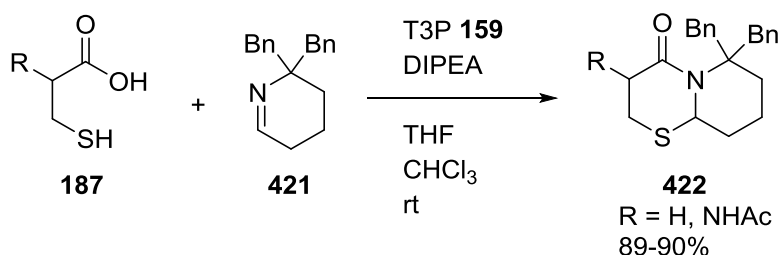
Scheme 130

3-Sulfanylpropanoic acid **190** has also been reacted with imines generated *in situ* by a tandem Staudinger / aza-Wittig reaction of azido sugars **423**.[175,176] The three reactions were done in one pot with microwave irradiation of the toluene solution (Scheme 131). The pathway is presumably the same as in Scheme 107 and similar to the reactions shown in Schemes 108 and 140.
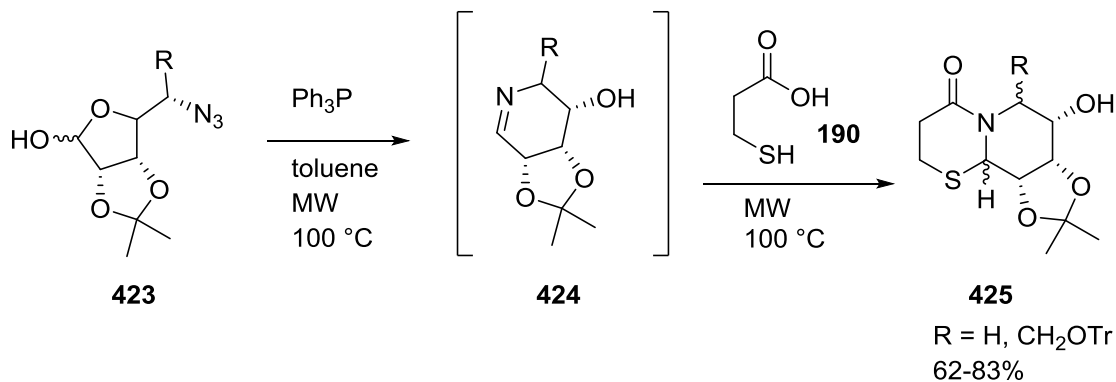
Scheme 131

2.4.12. Simultaneously *b*- and *e*-fused systems. 2-Chloropyridine-3-carbonyl chloride **244** was converted in a cascade reaction to the triheterocyclic imidazole product **425** in high yield (Scheme 132).[161] 1,10-Phenanthroline **300** was used as a ligand. The benzimidazole was also prepared.
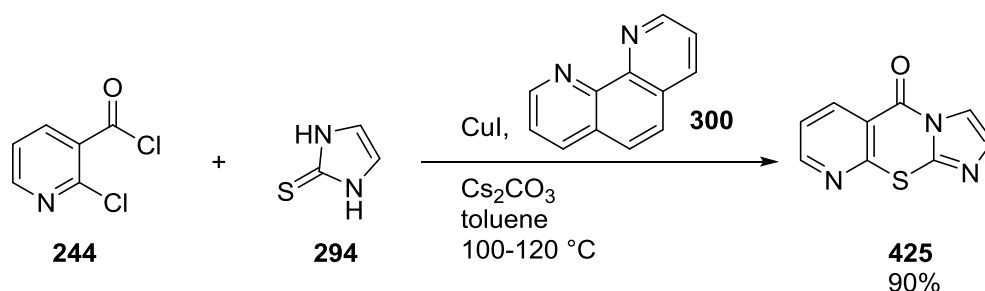
Scheme 132

In a less useful version, triheterocyclic compound **425** was synthesized in a two-step process (Scheme 133). First, thiourea **294** was reacted with 2-iodopyridine-3-carbonyl chloride **427** in the presence of CuI/tetrabutylammonium bromide (TBAB)/Cs$_2$CO$_3$/DMF at 130 °C. This gave the sulfide **428**, which was cyclized by treatment with EDC to give the imidazole **425** in low yield. A benzimidazole was also prepared in this manner.[160]
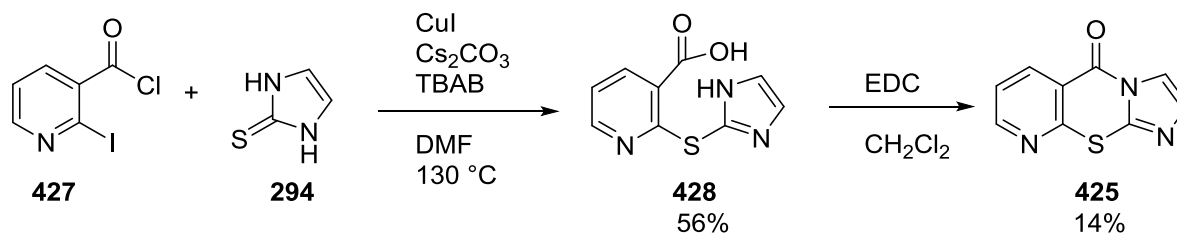
Scheme 133

As in Scheme 95, copper acetate has been used to prepare tricyclic benzimidazoles **430** and **432** (Scheme 134).[165]
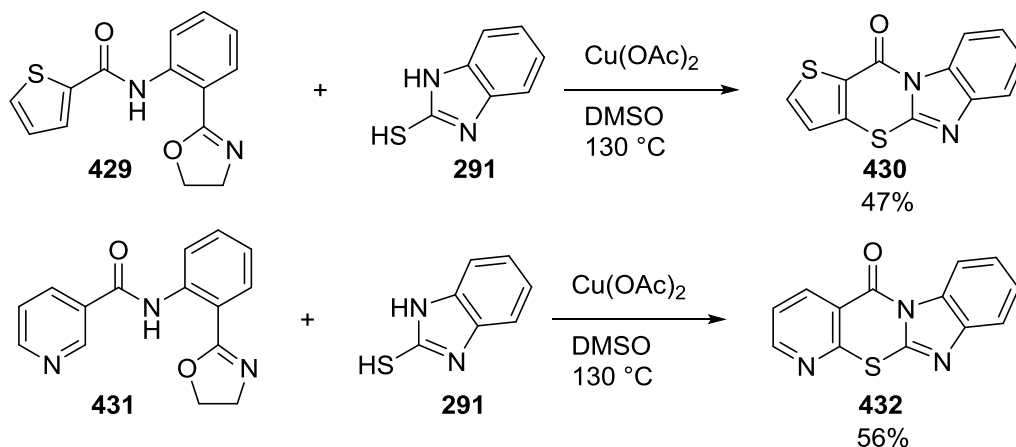
Scheme 134

Reaction of 2-chloroquinoline-3-carboxylic acids **433** with sulfanyltriazoles **434** led to tetracyclic compounds **435** (Scheme 135).[232]
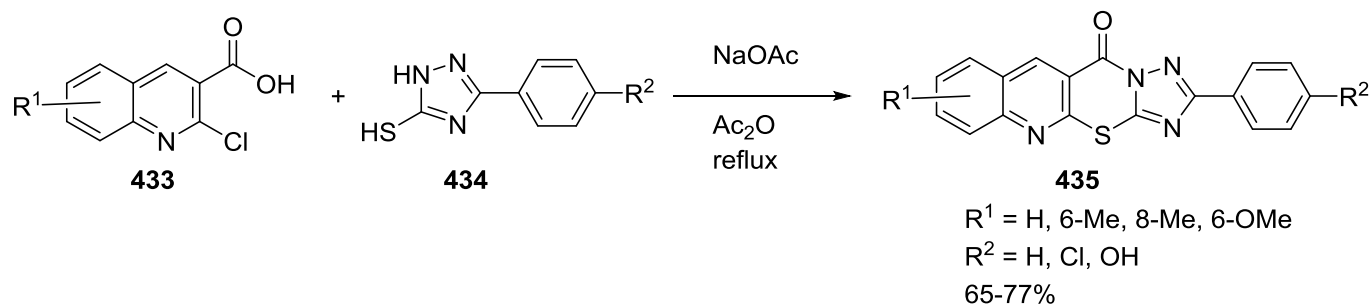
Scheme 135

Microwave-accelerated Pfitzinger reaction of isatin **257** with benzimidazole derivatives **436** under basic conditions gave tetracyclic compounds **437**. Both yields and rates were improved compared to conventional heating. Upon either heating the neat solid, microwave irradiation of the neat solid, or refluxing in DMSO, cyclization to pentacyclic **438** occurred (Scheme 136). Yields of **438** were similar in each case. [233]
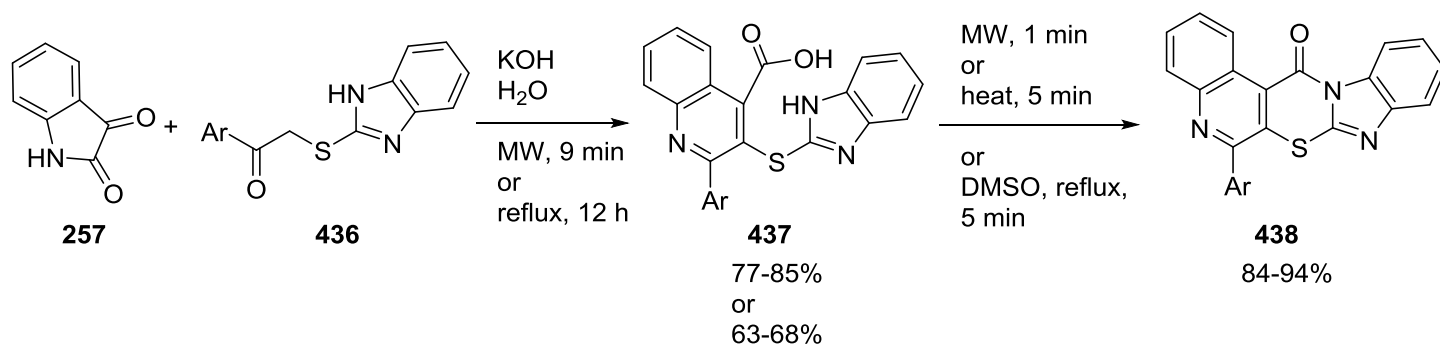
Scheme 136

Indole-fused 1,3-pyridothiazin-4-ones with an exocyclic C=C at the 2-position have been synthesized in two ways by the same group.[234] In one route, excess methyl 2-(chlorosulfanyl)benzoate **439** was reacted with indole **440** in DMF and 1,2-dichloroethane to give the *bis*-sulfide **441**. Compound **441** was cyclized to **442** by heating to 145 °C (Scheme 137). In the second route, 2-chloropyridine-3-carboxylic acid **443** was reacted with thioindole **444** in the presence of copper to give the sulfide **445**. Treatment of **445** with polyphosphate ester catalyst in CHCl$_3$ gave product **446 (**Scheme 138).
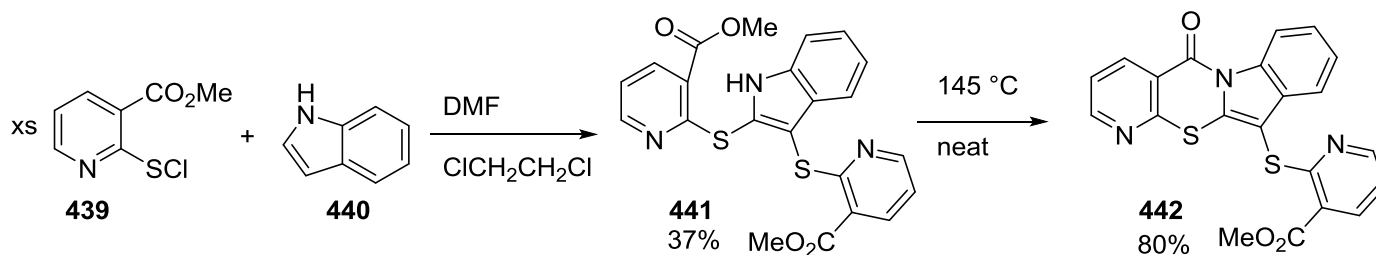
Scheme 137
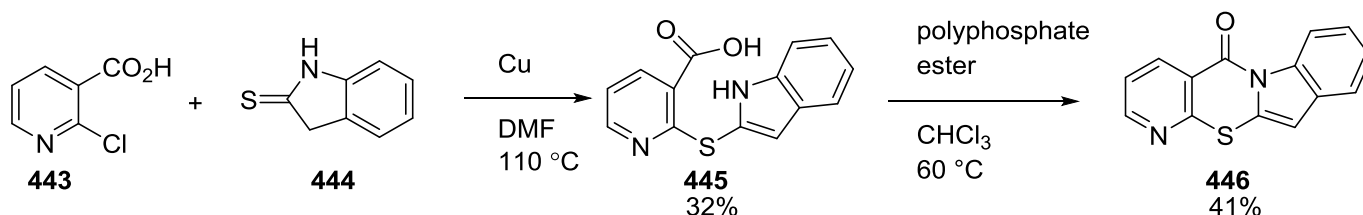
Scheme 138

Microwaves have been used to accelerate the reaction of 2-sulfanylpyridine-3-carboxylic acid **224** with cyclic imine **360** (Scheme 139).[5]
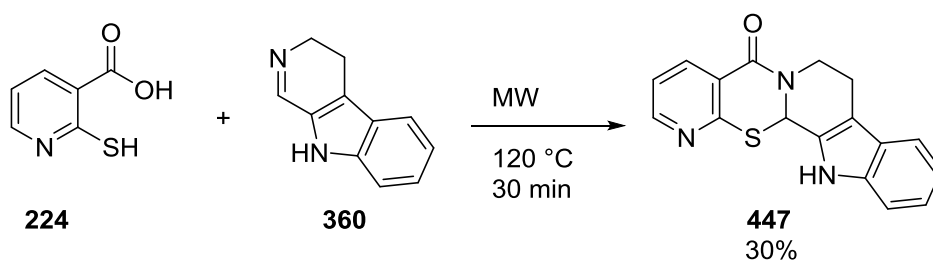
Scheme 139

Analogous to chemistry discussed earlier (Schemes 107, 108, and 131), 2-sulfanylpyridine-3-carboxylic acid **224** has been reacted with imines generated *in situ* by a tandem Staudinger/aza-Wittig reaction of sugars with an azide group.[175,176] The three reactions were done in one pot with microwave irradiation of the toluene solution (Scheme 140). Triphenylphosphine was added to 2-sulfanylpyridine-3-carboxylic acid **224** and the azide **422** and microwaved in toluene at 100 °C to generate the imine **423**. Unlike the earlier examples, DCC was added before the mixture was microwaved again in toluene at 100 °C to effect the cyclization to **448**. The pathway was similar to that of Scheme 107.
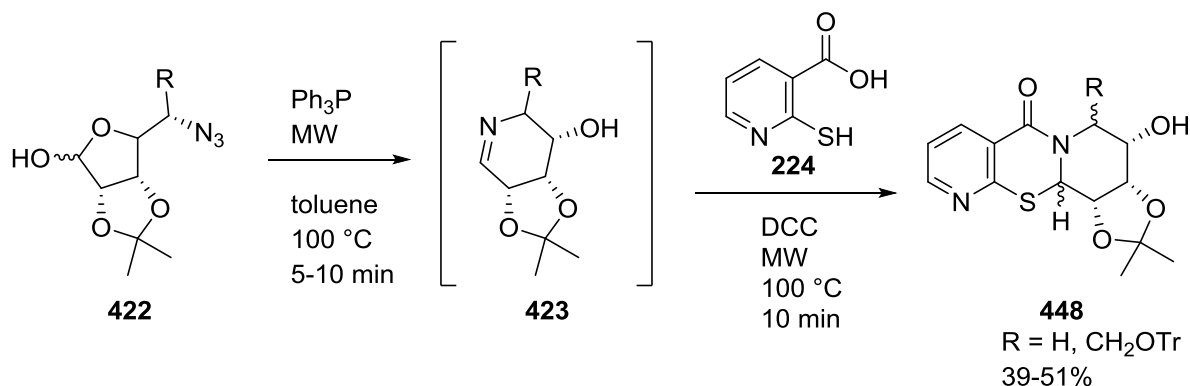
Scheme 140

2.5. Bridged systems. Formation of **450,** a 2,3,5,6-tetrahydro-1,3-thiazin-4-one with a bridged seven-membered nitrogen heterocycle, was achieved by acid-catalyzed intramolecular double cyclization of **449** (Scheme 141, stereochemistry not shown for simplicity). The acid catalyst released the starting material from the resin, removed the diethyl acetal and trityl protecting groups, and facilitated the nucleophilic attack of the amide nitrogen on the deprotected aldehyde to give the seven-membered cyclic iminium ion **451**, which was then attacked by the sulfur to form **450**.[235]
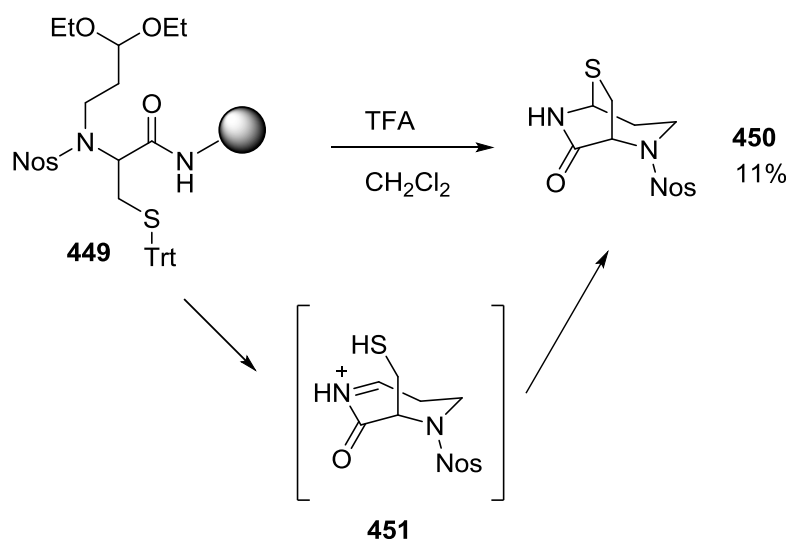
Scheme 141

Another method for constructing a bridged system started with **452**, which was converted into **454** by trimethylsilylation of the ethoxy group in **452** with TMSBr, followed by intramolecular attack of the benzyl sulfide to give bicyclic sulfinium ion **453**. Debenzylation then gave **454** (Scheme 142).[236]
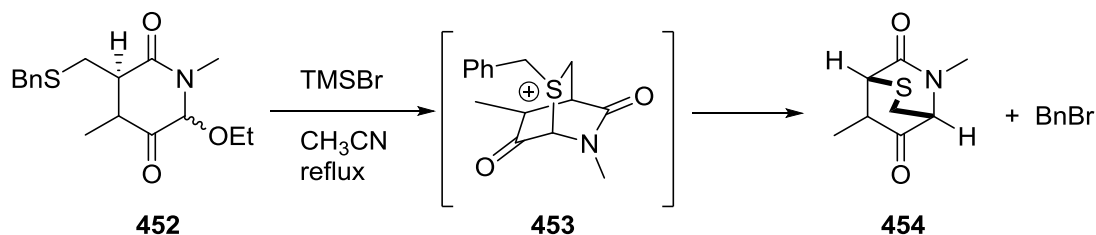
Scheme 142

Betaine **402** (see Scheme 123 for preparation) was reacted with 4-phenyl-1,2,4-triazoline-3,5-dione **455** to give the bridged 2,3,5,6-tetrahydro-1,3-thiazin-4,6-dione compound **456** (Scheme 143).[220]
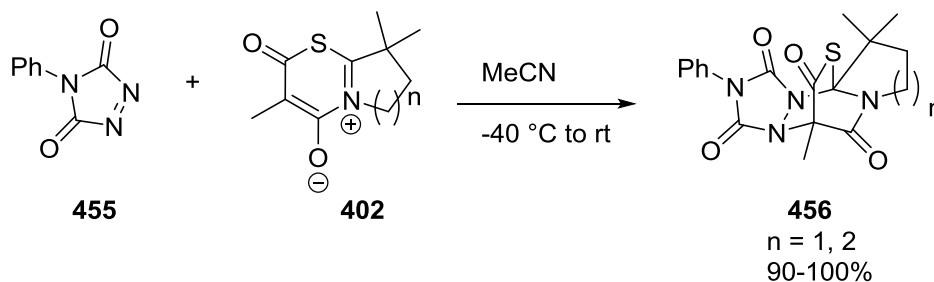
Scheme 143

Betaines such as compound **402** could also be reacted with carbon-carbon double bonds in various types of compounds and converted into bridged 2,3,5,6-tetrahydro-1,3-thiazin-4,6-dione compounds **458**, **460**, **462**, and **464** by dipolar cycloaddition (Scheme 144).[220]
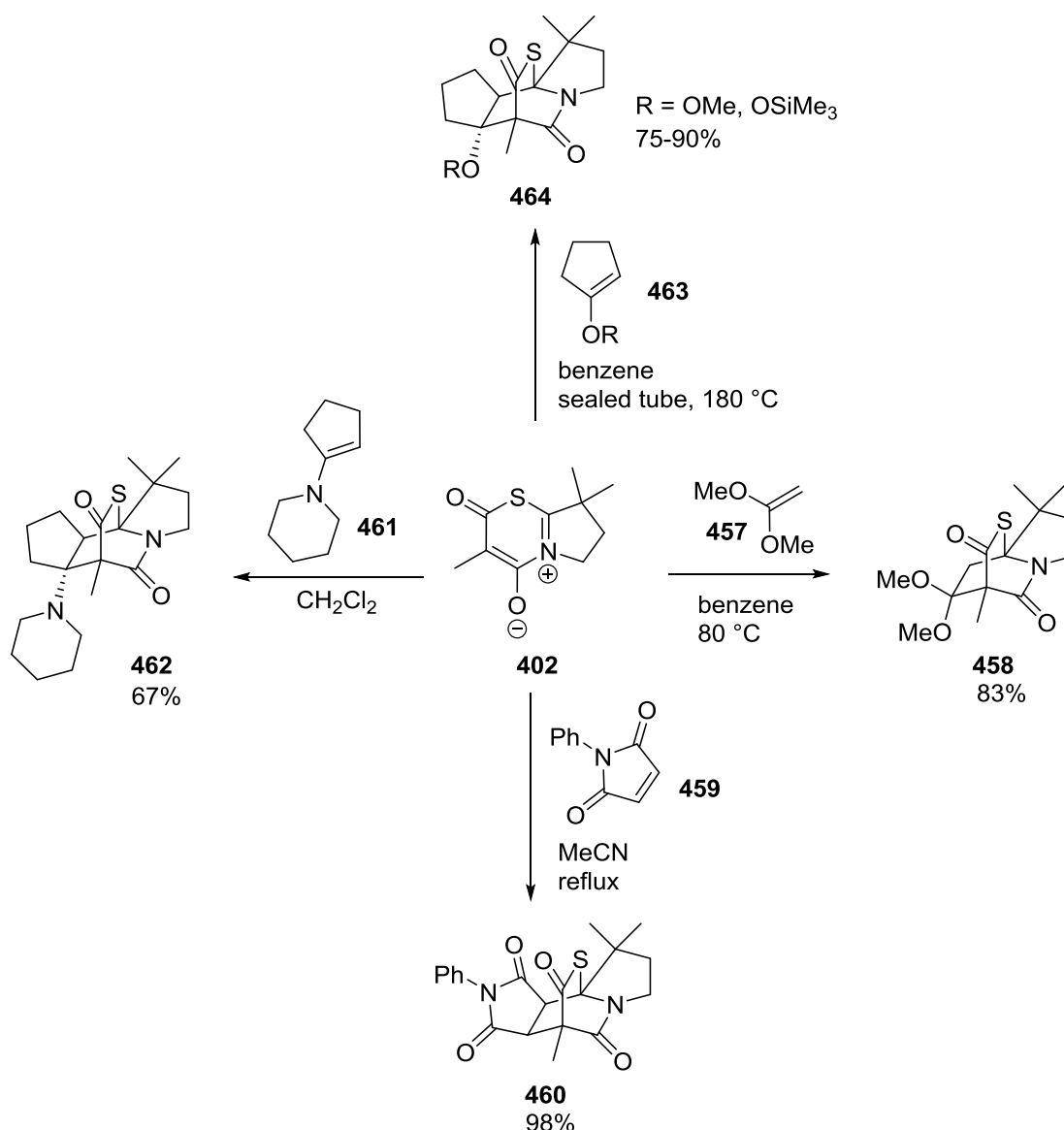
Scheme 144

Intramolecular dipolar cycloaddition of a betaine with a tethered alkene was also shown to give bridged systems, such as in Scheme 145.[220] Other variants were also reported.[224,237]

465   **466**
         98%
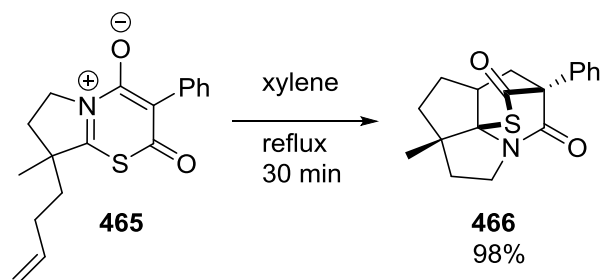
Scheme 145

Thiolactams, such as **467**, with a tethered alkene were reacted with carbon suboxide **402** to generate the betaine **468** *in situ*, which then cyclized as above to provide the bridged product **469** (Scheme 146).[237] Some other examples were provided as well.[237]

467   **402**   **468**   **469**
     67%
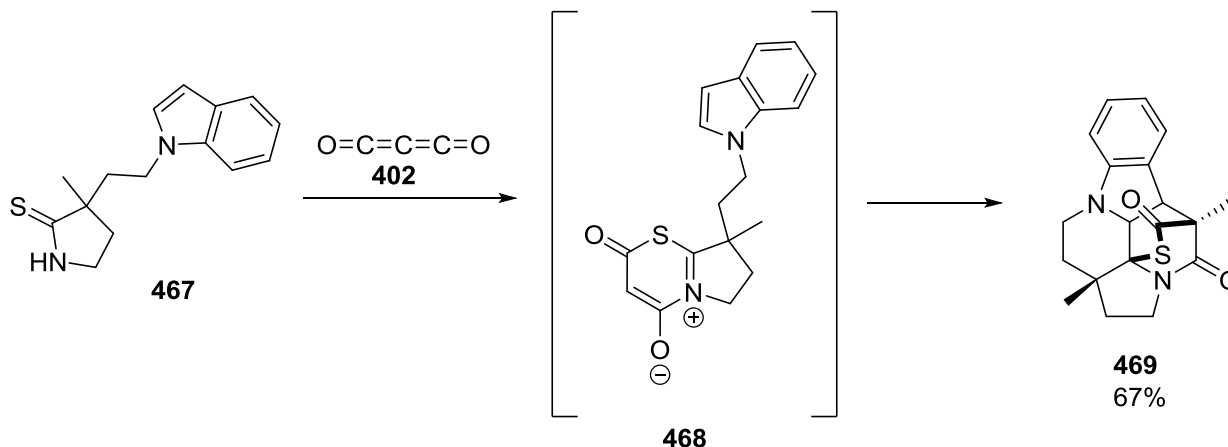
Scheme 146

3. Reactivity

3.1. Reactivity of the ring atoms with electrophiles

2-Imino-1,3-benzothiazin-4-ones **470** (see Scheme 171 for preparation) were *N*-alkylated by treatment with sodium methoxide followed by an alkyl halide **471** (Scheme 147).[238]
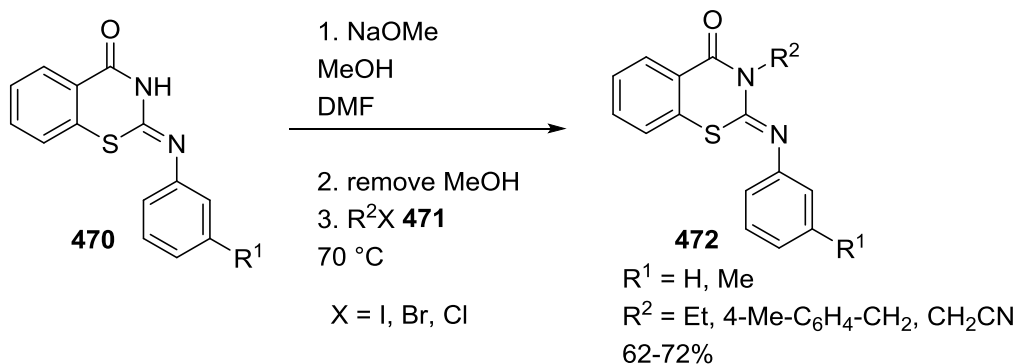
Scheme 147

2-Methylidene-1,3-benzothiazin-4-ones **473** were *N*-alkylated by phenacyl chlorides **474** with K_2CO_3 in DMF (Scheme 148).[239]
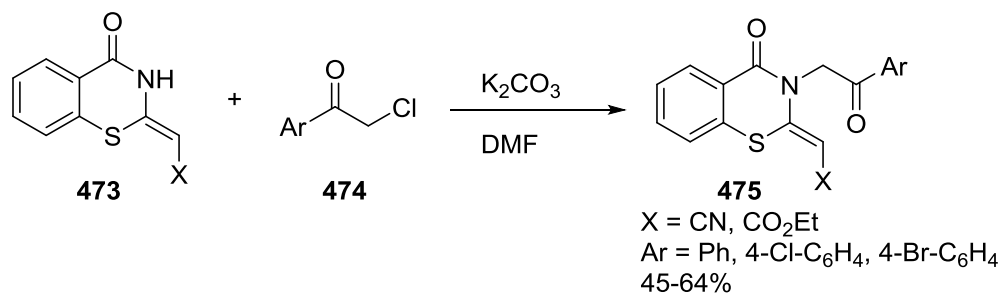
Scheme 148

Protection of the nitrogen of 2,3,5,6-tetrahydro-1,3-thiazin-4-one **476** with a Boc group (*N*-acylation) was done with the anhydride and DMAP (Scheme 149).[240]
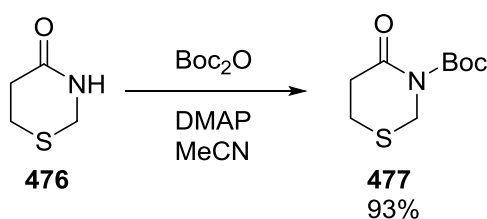
Scheme 149

b-Fused benzimidazo-2,3-dihydro-1,3-thiazin-4-one **478** when reacted with alkyl bromides **479** at 130 °C gave amide bond cleavage along with *N*-alkylation (Scheme 150).[241] However, when the analog **481** was reacted with benzyl bromide **482** in the same manner, cleavage of the S-C6 bond occurred to give **483** (Scheme 151).[241]
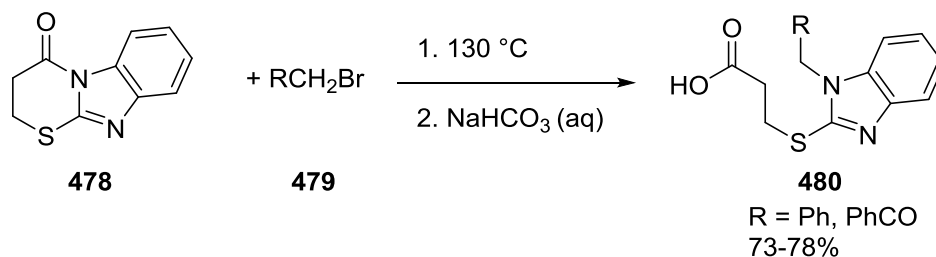
Scheme 150
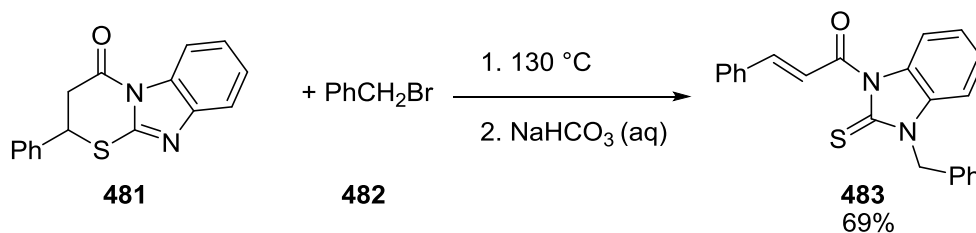
Scheme 151

Treatment of **481** with bromoacetophenone **61**, on the other hand, gave *N,N'*-dialkylated product **484** (Scheme 152).[241]
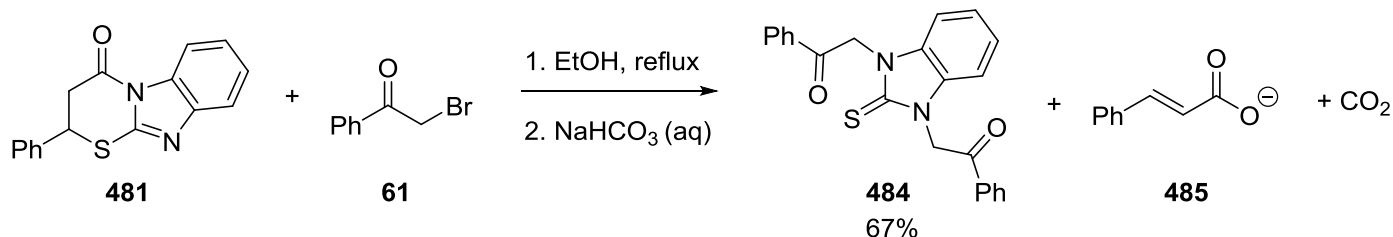
Scheme 152

Vinylation of *b*-fused 2-imino-5,6-dihydro-1,3-thiazin-4-one **486** with benzaldehyde **195** gave an exocyclic C=C moiety at the C-5 position, α to the C4 carbonyl (Scheme 153).[204] *b*-Fused 6-oxo-2-imino-5,6-dihydro-1,3-thiazin-4-one **489** was similarly vinylated with 4-nitrobenzaldehyde **488** (Scheme 154).[209]

Scheme 153

488   **489**   **490**
                                                                               40%
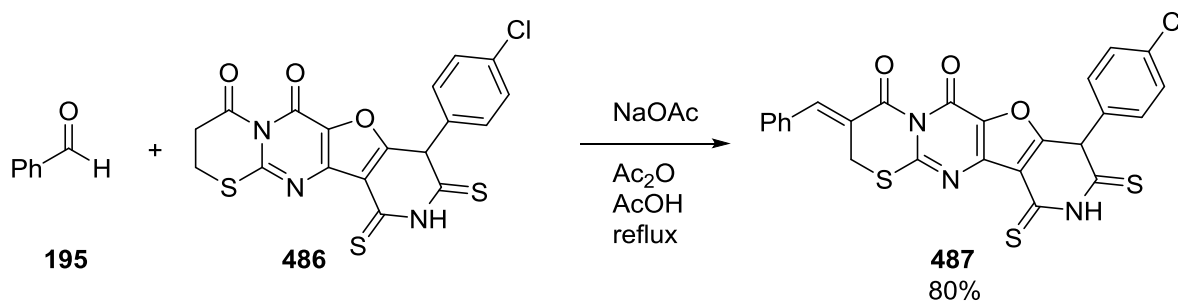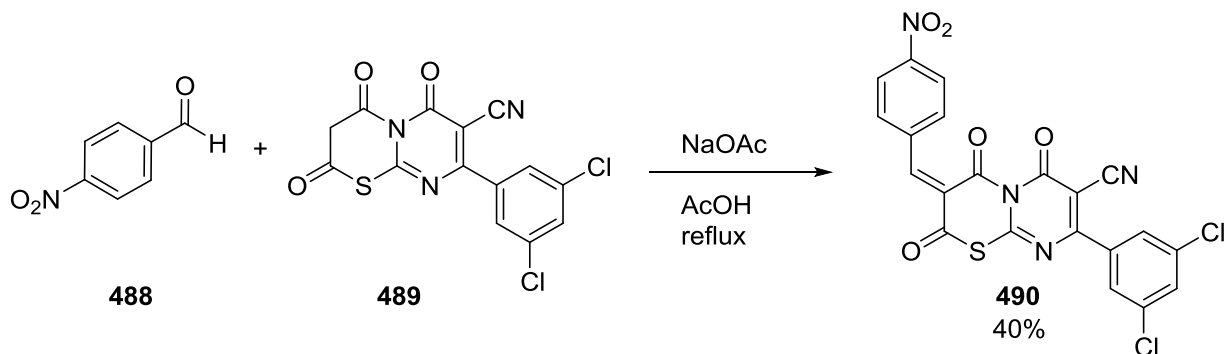
Scheme 154

Oxidation of *b*-fused benzimidazole **491** with hydrogen peroxide/acetic acid caused cleavage of the S-C2 and N3-C4 bonds, giving loss of 2-sulfopropanoic acid **492** (Scheme 155),[241] similar to reactivity previously reported for 2,3-dihydro-1,3-benzothiazin-4-ones.

491   **492**   **493**
                        69%   65%
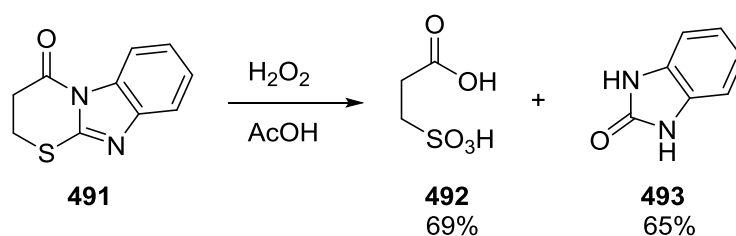
Scheme 155

However, when there was an aryl substituent on C6, treatment of *b*-fused benzimidazole 5,6-dihydro-1,3-thiazin-4-ones **388** with 30% hydrogen peroxide in acetic acid led to cleavage of the S-C6 and N3-C4 bonds (Scheme 156).[156,241]

388   **494**   **495**
                         Ar = Ph, 4-OMe-   59-71%
                         C_6H_4, 3-NO_2-C_6H_4
                         56-74%
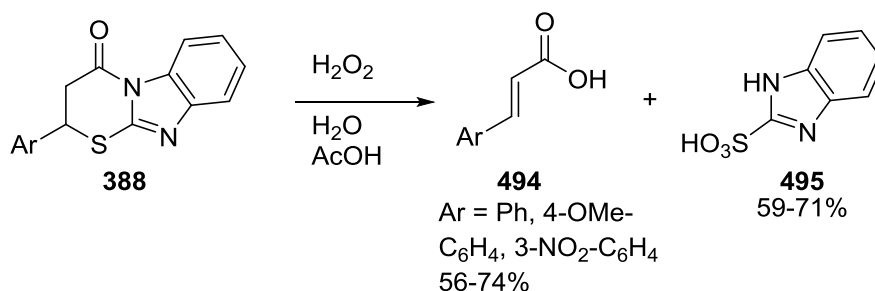
Scheme 156

Cleavage of the S-C6 bond in **481** was also the result of an attempt to make the methyl *p*-toluenesulfonate salt **497**, which evidently decomposed to give **498** (Scheme 157).[156]

481   **496**   **497**   **498**
                                          64%
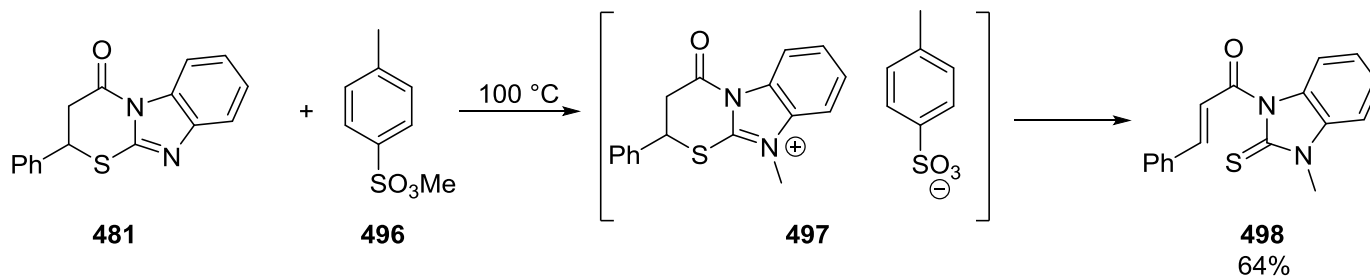
Scheme 157

The sulfur in various 2,3-dihydro-1,3-thiazin-4-ones was oxidized selectively to the sulfoxides **500-503** using Oxone® (Scheme 158).[242-245]

499   **500**
            99%

501   **502**   **503**
70%   68%
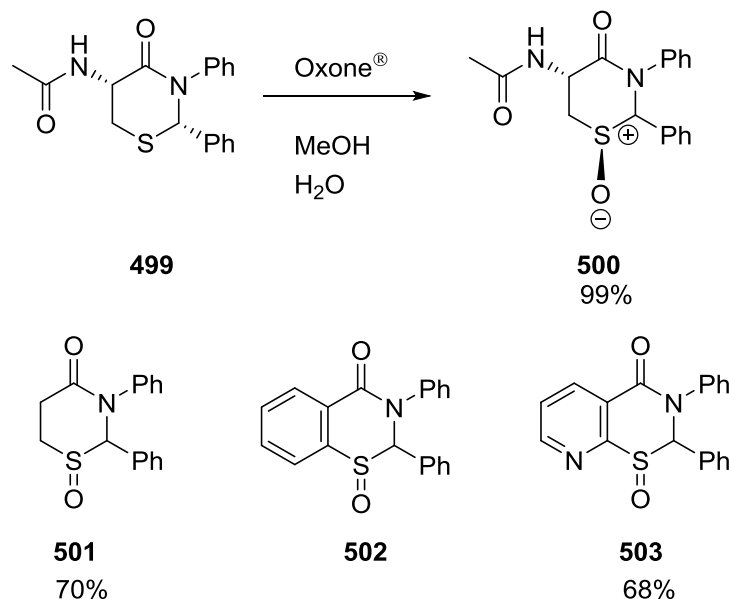
Scheme 158

Sulfoxidation of 2,3-dihydro-1,3-benzothiazin-4-one **504** with iodosobenzene in the presence of a chiral manganese catalyst **505** gave the desired sulfoxide **506**, but in only 13% ee (Scheme 159).[246]

504   **506**   **Mn catalyst**
            90% yield   **505**
            13% ee
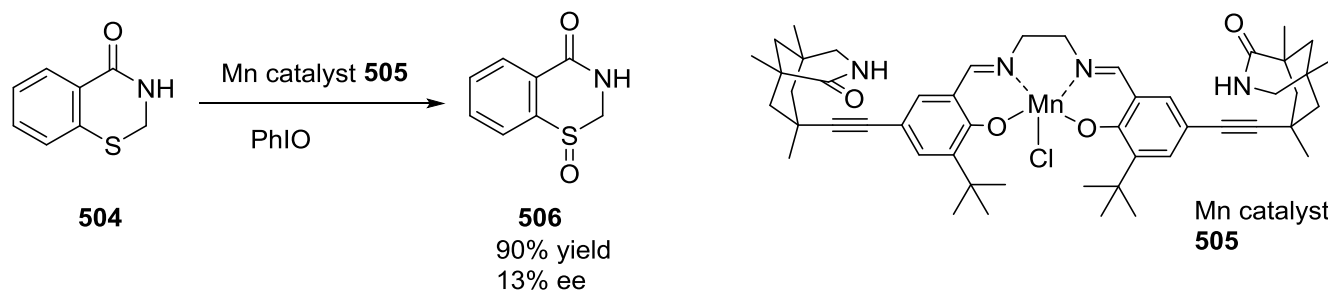
Scheme 159

Oxidation of sulfides **507** to the sulfones **508** was done with a tungsten catalyst, similar to a method noted in the prior review (Scheme 160).[5]

507

508
R = H, OMe
63-78%
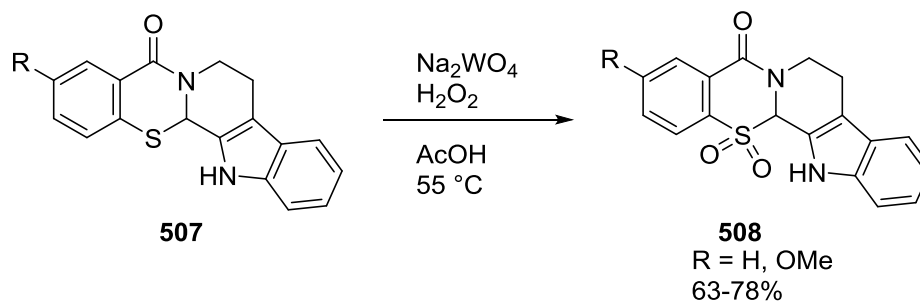
Scheme 160

KMnO$_4$ with H$_2$SO$_4$ in H$_2$O/CH$_2$Cl$_2$ was used to oxidize sulfide **509** to sulfone **510** (Scheme 161).[211]

509

510
58%
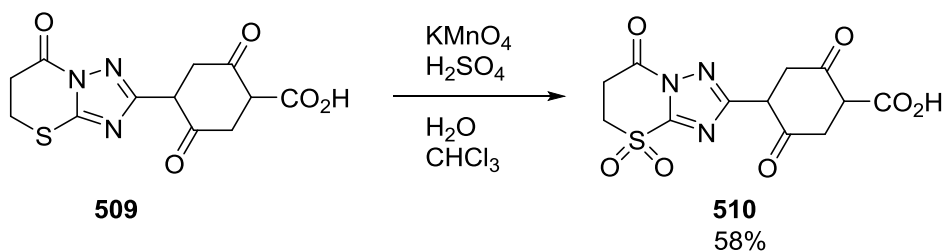
Scheme 161

The triphenyltin chloride complex **513** of 2,3-diphenyl-2,3,5,6-tetrahydro-1,3-thiazin-4-one **511** was readily prepared (Scheme 162).[247] However, attempts to make the complex of 2,3-diphenyl-5,6-dihydro-1,3-benzothiazin-4-one **514** gave only the sulfoxide **502**.[244]

511   **512**   **513**
45%
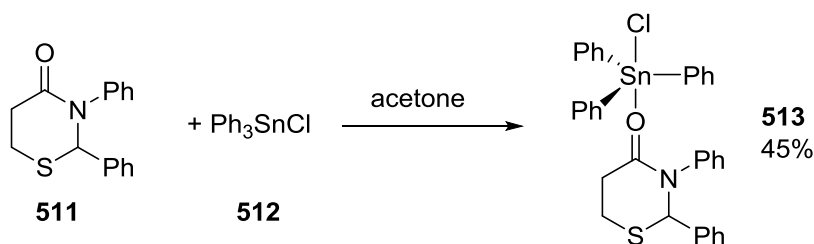
Scheme 162

Oxidation of the 5,6 C-C by dehydrogenation was shown in Schemes 7, 18, and 87. Reaction of 5-cyano-6-amino-1,3-thiazin-4-ones **72** with β-ketoalkyl halides **515** and triethylamine gave thienopyrimidone products **516**.[39] This was explained by base-promoted Dimroth rearrangement to give an exo sulfur anion **518**, which then attacked the alkyl halide **515**. The subsequently formed enolate ion **520** then attacked the nitrile, leading to the fused ring **516** (Scheme 163).[39] The formation of compounds **518** had been earlier demonstrated by hydrolysis of **72** with aqueous KOH, which gave the potassium salts of **518** (R^1 = Et, Ph; R^2= H; R^3 = Ph, 4-NO$_2$-C$_6$H$_4$; 75-82%).[37]

R^1 = Ph, Et
R^2 = H, Me
R^3 = Ph, 4-MeO-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, Me, 2-thienyl, 2,3-dihydro-1,4-benzodioxan-6-yl
R^4 = Me, *t*-Bu, Ph
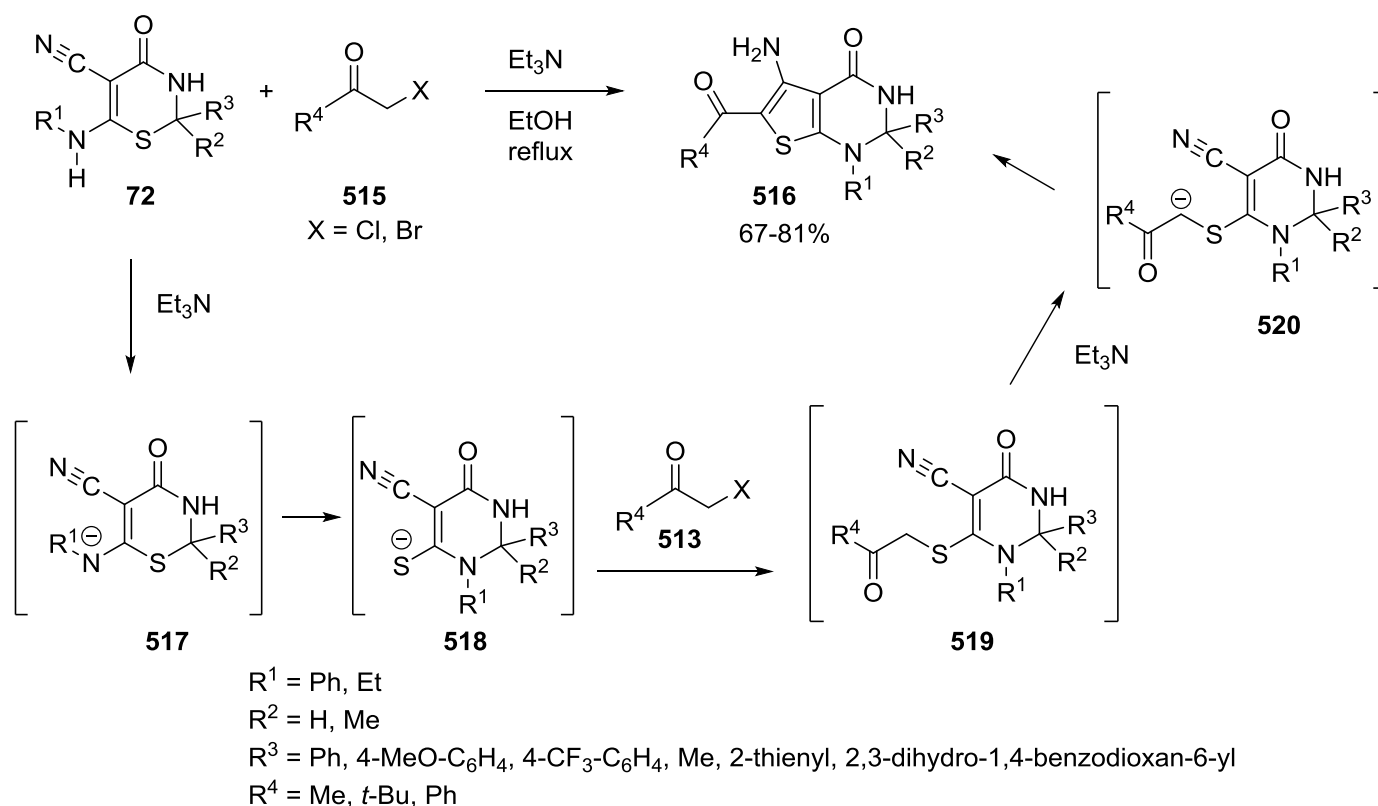
Scheme 163

When 6-anilino-5-cyano-1,3-thiazin-4-one **521** was treated with bromoacetonitrile **522** and aqueous KOH, a product **523** similar to **516** was obtained (Scheme 164).[38] The mechanism was presumed to be similar to Scheme 163, with an intermediate akin to **516**. Other examples were demonstrated.[17,41]
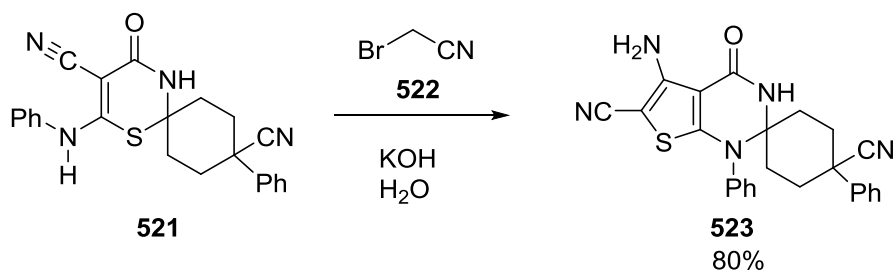
Scheme 164

When the reaction in Scheme 163 had an adamantylidene group at C2 (**524**), a different outcome resulted due to steric hindrance (Scheme 165).[39] It was proposed that the thiophene **527** therefore formed first.
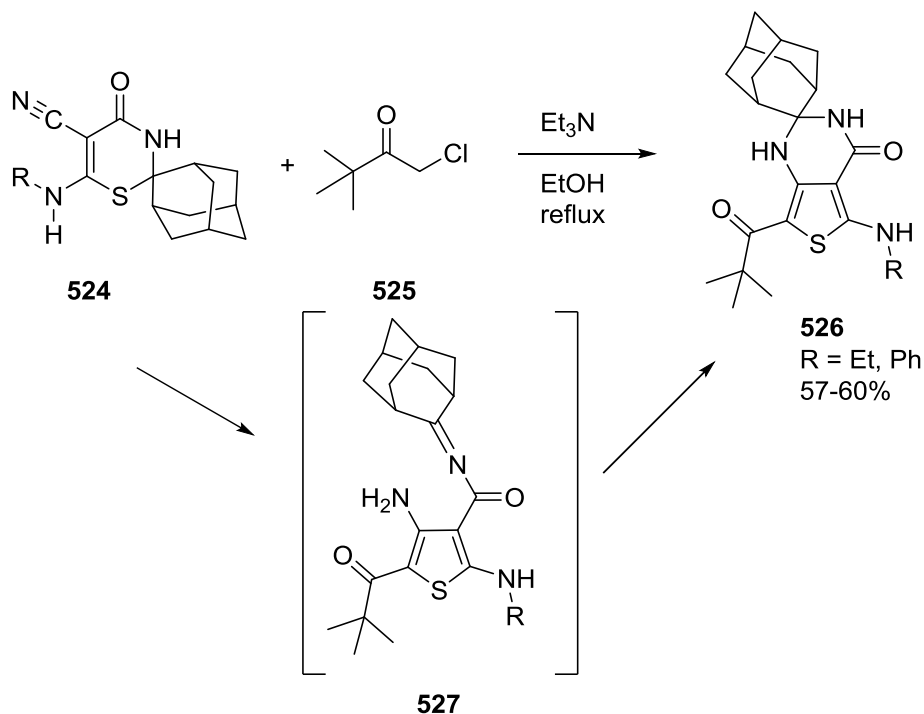
Scheme 165

When **72** was treated with alkyl halides and base, the thienyl ring did not form.[17,37.38.41] Using benzyl chloride **528** with Et$_3$N/EtOH[37,38,41] or aqueous KOH,[17] the reaction stopped after *S*-alkylation. Some examples are shown in Scheme 166.[37]

R^1 = Ph
R^2 = H, Me
R^3 = Me, *i*-Pr, 4-OMe-C$_6$H$_4$
63-69%
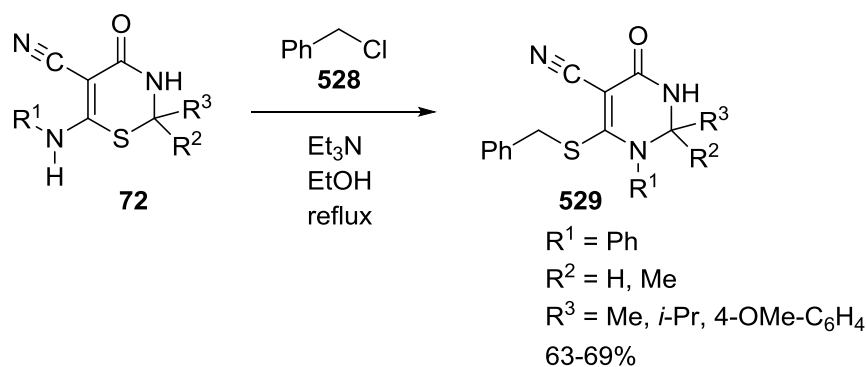
Scheme 166

When compound **521** was reacted with ethyl iodide **530** and K$_2$CO$_3$, the product was ethylated at both S and N (Scheme 167).[38] However, the phenylene-bridged *bis*-(2,3-dihydro-1,3-thiazin-4-ones) **532** under the same conditions only alkylated the sulfurs (Scheme 168).[17] Another compound similar to **521** also gave only *S*-ethylation.[41]
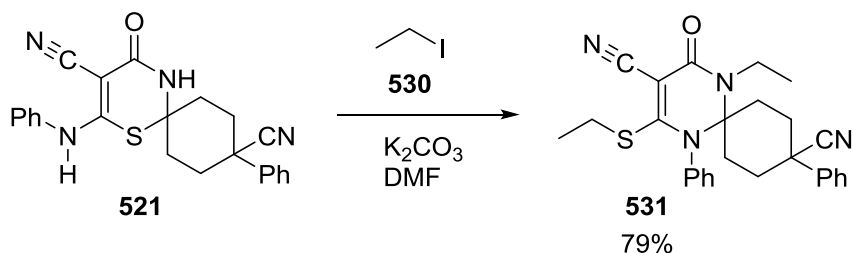
Scheme 167
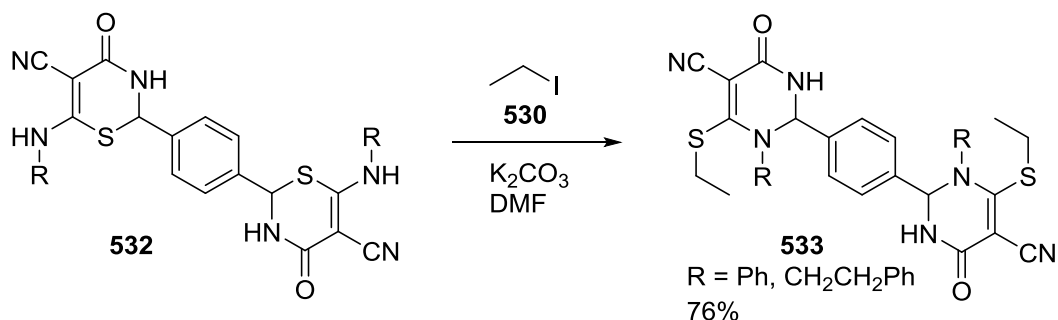
Scheme 168

Dimethyl sulfate in aqueous KOH similarly gave the *S*-methylated products (some examples shown in Scheme 169).[17,37,38,41] When the C2 substituent on **72** was bulky adamantanyl, dimethyl sulfate/KOH(*aq*) gave ring opening and loss of adamantanone.[37]

R[1] = Me, Et, Ph
R[2] = H, Me
R[3] = Me, Ph
R[2],R[3] = 6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl,
-(CH$_2$)$_4$-, 2',3'-dihydro-1,4-benzodioxin-6'-yl
60-78%
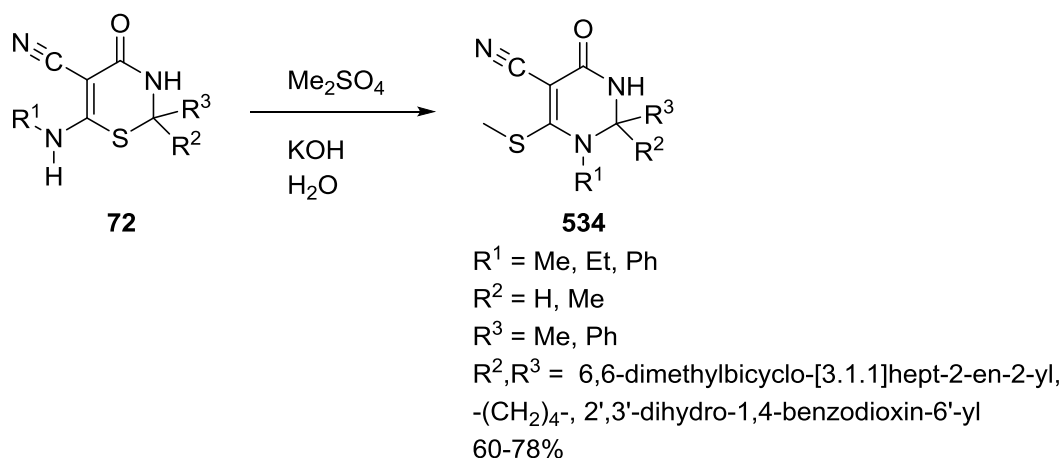
Scheme 169

When ethyl bromoacetate/aqueous KOH was used, some cases produced thienyl compounds like **516** and some cases stopped at *S*-alkylation products like **519**.[17,38,41]

Bridged compound **454** (see Scheme 142 for preparation) was selectively deprotonated by LDA at the bridgehead C2 position of the 1,3-thiazin-4-one ring, which was α to another carbonyl. Treatment with benzaldehyde **195** gave the alkylated product **535**. After two-step reduction of the alcohol, compound **536** was deprotonated again with lithium diisopropylamide (LDA), and elimination gave the thiolate ion **537**, which was trapped as the trityl disulfide **539** (Scheme 170).[236]
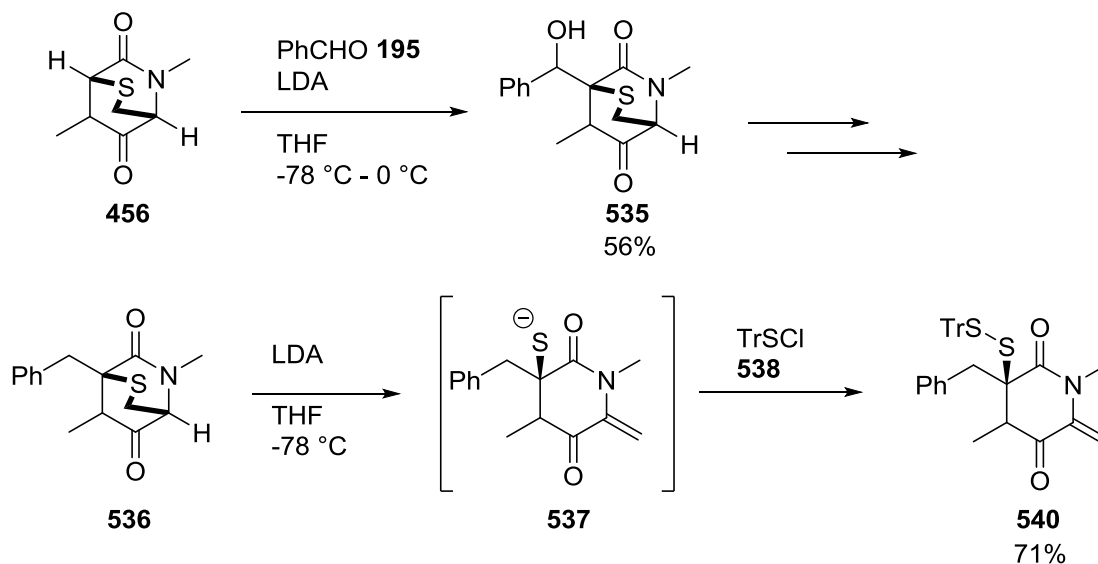
Scheme 170

3.2. Reactivity of the ring atoms with nucleophiles

Reaction of the 2-amino-1,3-benzothiazin-4-one **540** with anilines **201** and HCl at 150 °C gave compounds **470** (Scheme 171).[238]
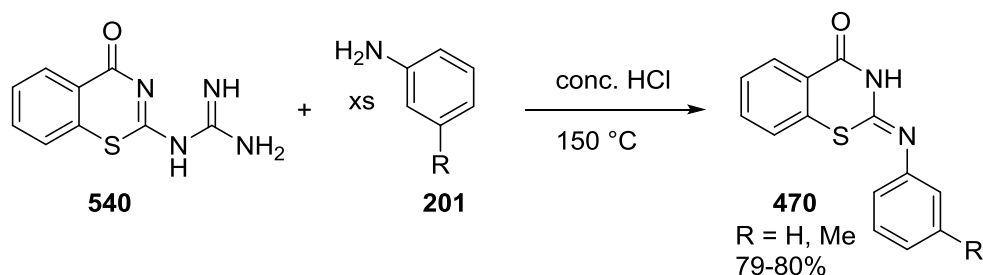
Scheme 171

Reaction of the tricyclic 1,3-benzothiazin-4-one **334** with propylamine **541** in refluxing dioxane effected ring opening *via* cleavage of the N3-C4 bond (Scheme 172).[171]
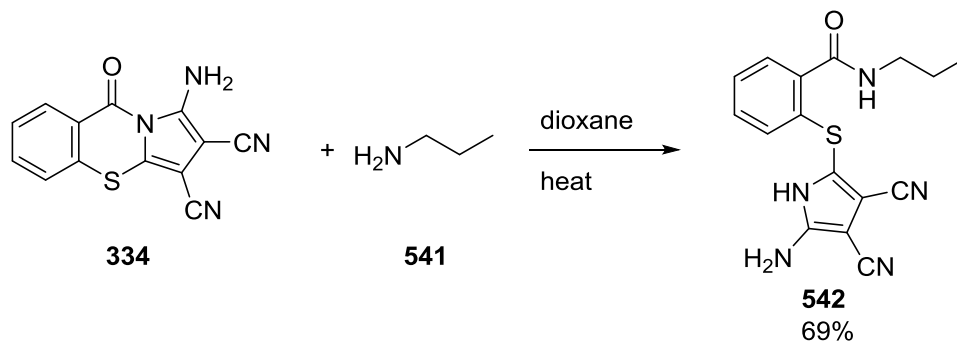
Scheme 172

Similarly, reaction of *b*-fused benzimidazole **491** with ammonia, hydrazine or benzylamine in refluxing ethanol gave products **543** (Scheme 173).[241] The same reaction with a 6-aryl group (Ph, 4-OMe-C$_6$H$_4$) on the

1,3-thiazin-4-one ring gave products **455** when R = H and NH$_2$ (70-86%) (Scheme 173), but benzylamine caused cleavage of both the S-C6 and N3-C4 bonds.[241]
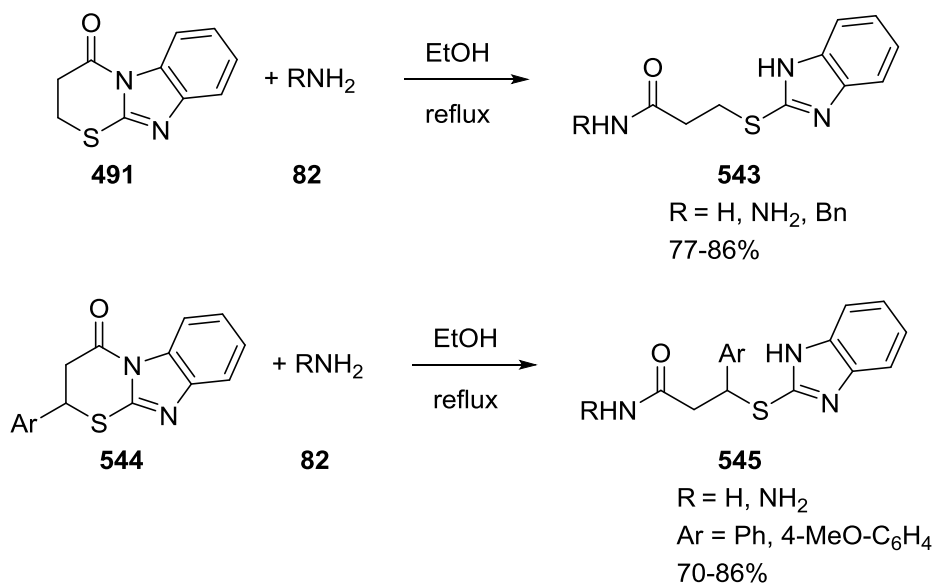
Scheme 173

b-Fused triazolo-compounds **546** also reacted differently with amines depending on the conditions and the structure of **546** (Scheme 174).[248] In refluxing ethanol, N3-C4 cleavage occurred, giving **547**. At higher temperatures, refluxing in the amine **82** alone, when R^1 = H, S1-C6 bond cleavage gave **548**. When R^1 ≠ H however, both cleavages occurred, giving **549** and **548**.
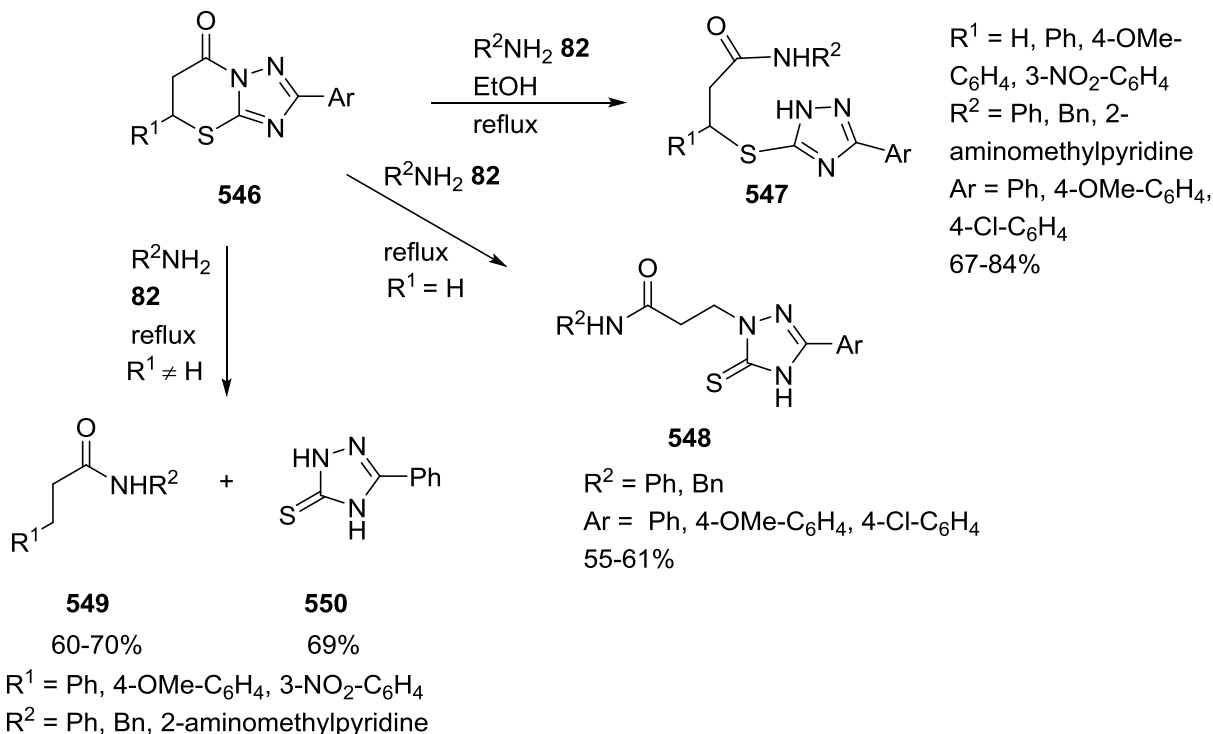
Scheme 174

Reaction of *b*-fused quinazole compound **551** with hydrazine **552** in refluxing ethanol gave **553**, in which both the S-C2 and N3-C4 bonds had been broken (Scheme 175).[192]
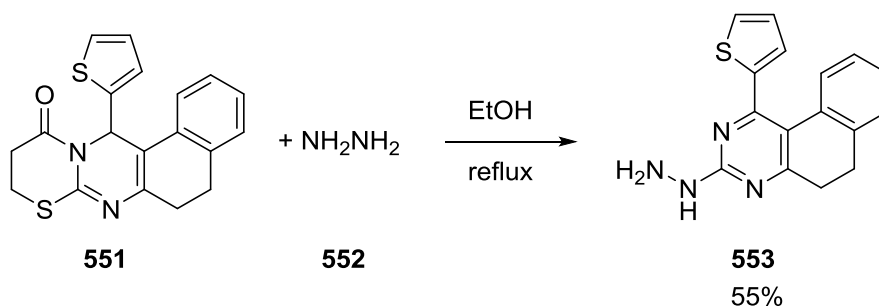
Scheme 175

Acidic hydrolysis of the 2-ethoxy-2,3,5,6-tetrahydro-1,3-thiazin-4-one **213** (see Scheme 65 for synthesis) with aqueous HCl produced ring-opened compound **554** (Scheme 176).   The proposed pathway was elimination of ethanol, then addition of ethanol to the carbonyl, followed by N3-C4 bond cleavage and hydrolysis. Boron trifluoride heated in toluene, followed by addition of water, also worked.[143]
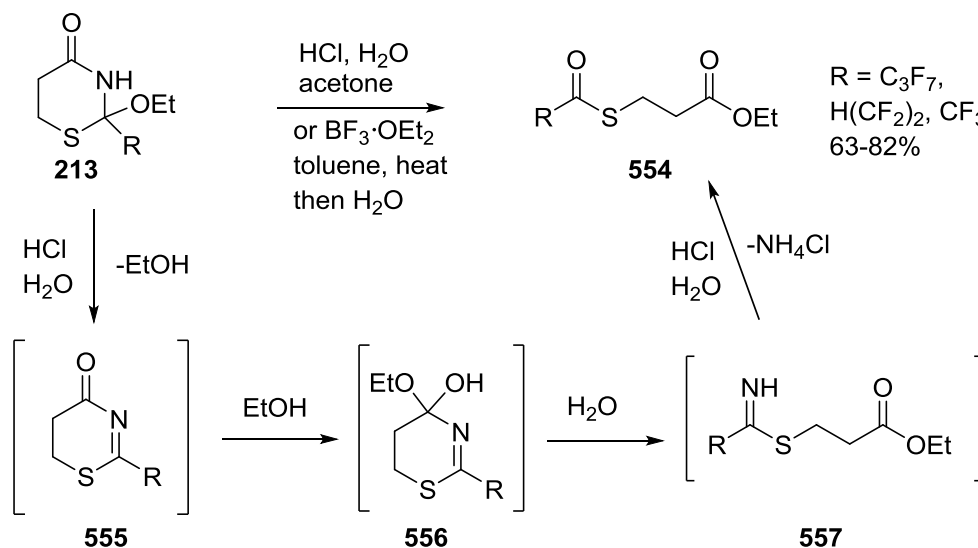
Scheme 176

Amide hydrolysis of triazole compounds **387** took place in 95 °C water (Scheme 177).[214]

387

558

R^1= Ph, 3,4-(MeO)$_2$-C$_6$H$_3$, 4-NO$_2$-C$_6$H$_4$,
4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, 1-naphthyl, 3,4-
methylenedioxyphenyl, 2-thienyl
71-94%
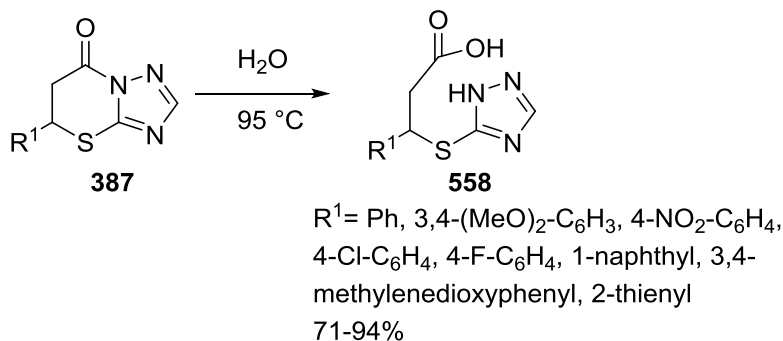
Scheme 177

Basic methanolysis of 6-carboxymethyl-1,3-thiazin-4-one **559** generated dimethyl acetylenedicarboxylate **558** (Scheme 178). However, treatment of **560** with methanol and sulfuric acid hydrolyzed the ester to the acid, leaving the ring unaffected.[156]

559

560

561
59%
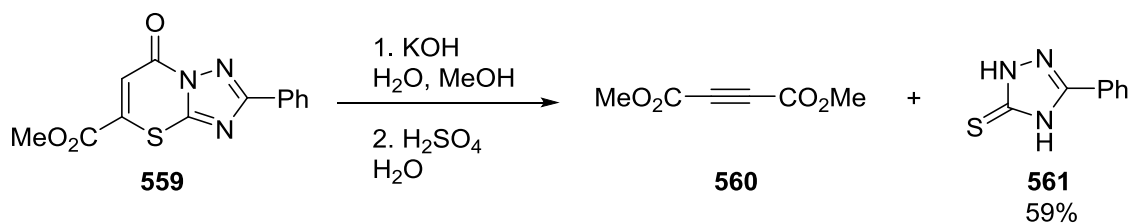
Scheme 178

Basic hydrolysis of *b*-fused benzimidazoles **388** broke the N3-C4 bond to give the carboxylic acids **562** (Scheme 169).[156]

388

562

Ar = Ph, 4-OMe-
C$_6$H$_4$, 3-NO$_2$-C$_6$H$_4$
66-76%
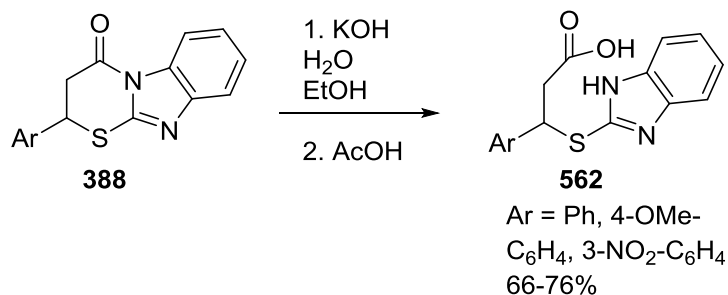
Scheme 179

Reaction of 2,3-dihydro-1,3-benzothiazin-4-one **165** (see Scheme 47 for preparation) with P$_2$S$_5$ and pyridine gave the thiolactam **563** (Scheme 180).[108] Two similar conversions were done with P$_2$S$_5$ in hexamethyldisiloxane (HMDSO) at 120 °C with microwave irradiation (Scheme 181).[108]

Scheme 180

R = 5-pyrimidyl, 3-OMe-C$_6$H$_4$
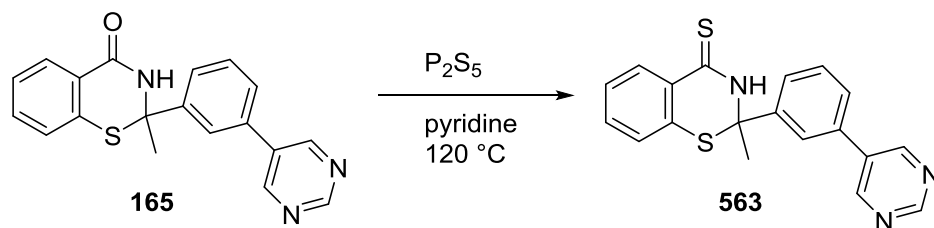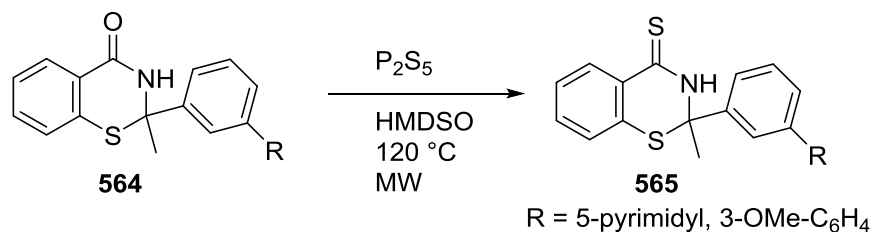
Scheme 181

Reduction of the C2-N3 double bond with NaBH$_4$ was shown in Scheme 50.

3.3. Other reactions of the ring atoms

The 4,6-dione **566** was diazotized at C5 and then reacted with cyclohexene in a rhodium-catalyzed cyclopropanation reaction (Scheme 182).[224]
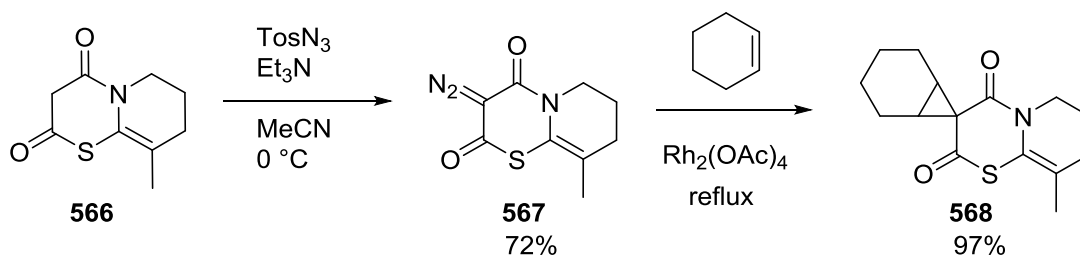
Scheme 182

Bridged heterocycles such as **466** and others in Schemes 144 and 145 upon sufficient heating lost COS **570** (Scheme 183).[220,224,237]
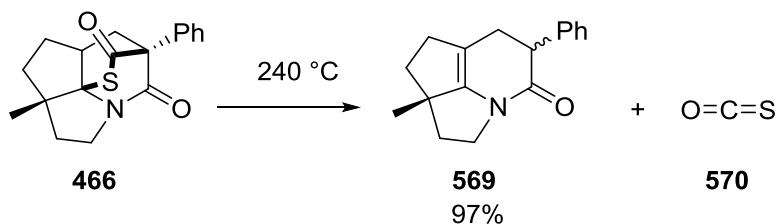
Scheme 183

4. Conclusions

Clearly, there have been many advances in the chemistry of these important heterocycles since 1994. Although the review of the syntheses was broken into different types of structures, there is a lot of commonality in the approaches. Thus, while the reader may be looking for methods to make one type of ring, the answer may be found in approaches used for another type of 1,3-thiazin-4-one. Commonality can also be seen in the review of the reactions, and these were in fact organized by reaction type. Thus, a broad view of the 1,3-thiazin-4-ones should be taken by researchers in this area.

Acknowledgements

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Author's Biographies

Lee J. Silverberg was born in 1963. He attended college at George Washington University in Washington. D.C., earning a B.S. in Chemistry with a minor in Journalism. He then went to the University of Delaware for graduate work in Organic Chemistry. He worked with two advisors while there. From 1987-1989 he trained with Prof. Richard F. Heck, doing palladium-catalyzed reactions of alkynes with vinyl and aryl halides. Upon Prof. Heck's retirement, he went to the lab of Prof. Douglass F. Taber, where he studied ruthenium-catalyzed enantioselective hydrogenation of β-keto esters and completed a synthesis of natural product (+)-brefeldin A. After graduation in 1991, he went to work for Bristol-Myers Squibb in process research and development. He later worked for Johnson Matthey Pharmaceutical Materials and Merck, successfully developing processes for many APIs along the way. In 2009, Dr. Silverberg reentered academia, teaching one semester at Camden County College in New Jersey before joining Pennsylvania State University, Schuylkill Campus, in Fall 2009. He is still there and currently an Associate Professor. He teaches General Chemistry and Organic Chemistry. His research is in the area of heterocyclic compounds and his lab group is exclusively undergraduates.

Quentin J. Moyer was born in 1995 and grew up in Schuylkill County, PA where he ultimately attended college at the Pennsylvania State University Schuylkill Campus. He entered college in 2014 as a nursing student but chose to study biology after finishing a semester of clinical education at the Reading Hospital School of Health Sciences. He became affiliated with Lee Silverberg's laboratory soon after in 2016, contributing to projects involving the 1,3-thiazin-4-one scaffold. He is currently a first-year medical student at Harvard and contributing to clinical research at the Boston Children's Hospital Department of Plastic Surgery. He enjoys performing with his bands, short film production, and his old Volvos.