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SYNTHETIC ROUTES TOWARDS THIAZOLO[1,3,5]TRIAZINES (REVIEW)[1]

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Abstract – The present review summarizes information on the synthetic approaches to thiazolo[3,2-*a*][1,3,5]triazines and polyfused systems bearing this heterocyclic core since the first report on this structure in 1887. The methods allowing access to the heterocyclic systems comprising isomeric thiazolo[3,4-*a*][1,3,5]triazine scaffold are also included in the review. Data concerning potential applications of the thiazolo[1,3,5]triazines, particularly as biologically active agents are discussed.

Dedicated to Professor Viktor E. Kolla with my best wishes on the occasion of his 85th birthday

CONTENTS

1. INTRODUCTION

In this review, we summarized existing methods of the synthesis of the compounds comprising thiazolo[3,2-*a*][1,3,5]triazine (**A**) and thiazolo[3,4-*a*][1,3,5]triazine (**B**) nuclei (Figure 1) as well as their biological activity and applications. Information on the preparation of related fused heterocyclic system (**C**) with 1,2-thiazole (isothiazole) instead of 1,3-thiazole ring is not available in the literature.

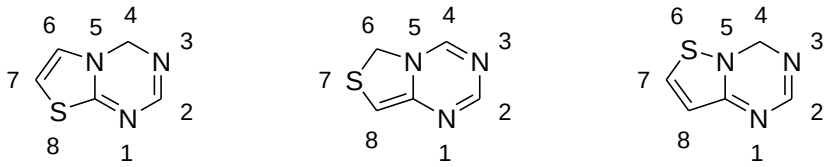
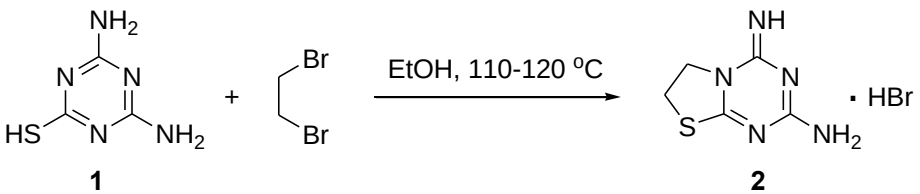


Figure 1

The synthesis of first thiazolo[3,2-*a*][1,3,5]triazine derivative was described by Rathke in 1887.[2,3] He reported the reaction of thioammeline (**1**) with 1,2-dibromoethane that afforded **2** (Scheme 1). However, this work was not continued and it took more than 70 years for thiazolo[3,2-*a*][1,3,5]triazines to come back to the scene. Until now, a number of effective synthetic procedure have been developed for the preparation of diversely substituted thiazolo[3,2-*a*][1,3,5]triazines. They are discussed in Section 2 of this review.



Scheme 1

During last decade, significant interest has been developed towards the biological activity investigation of compounds with the thiazolo[3,2-*a*][1,3,5]triazine heterocyclic core. The attempted herein systematization of the available synthetic methods for the preparation of these compounds aims to facilitate further investigation in this emerging field of research.

There no data on the synthesis of compounds possessing two-ring system **B**, thus Section 3 covers the preparation of more complex polyfused systems comprising thiazolo[3,4-*a*][1,3,5]triazine structure (**B**).

2. SYNTHESIS OF THIAZOLO[3,2-*a*][1,3,5]TRIAZINES AND THEIR POLYFUSED ANALOGUES

The general methods of synthesis of thiazolo[3,2-*a*][1,3,5]triazines can be categorized into: (1) annelation of the 1,3,5-triazine ring onto a thiazole scaffold, (2) annelation of the thiazole ring onto a 1,3,5-triazine scaffold and (3) formation of both rings in the same reaction.

2.1. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines by annelation of the 1,3,5-triazine ring onto a thiazole scaffold.

The annelation of the 1,3,5-triazine ring onto a thiazole scaffold is the most explored and developed approach for the synthesis of thiazolo[3,2-*a*][1,3,5]triazines. It is further subdivided in this review on the basis of the reaction type and structure of the building blocks.

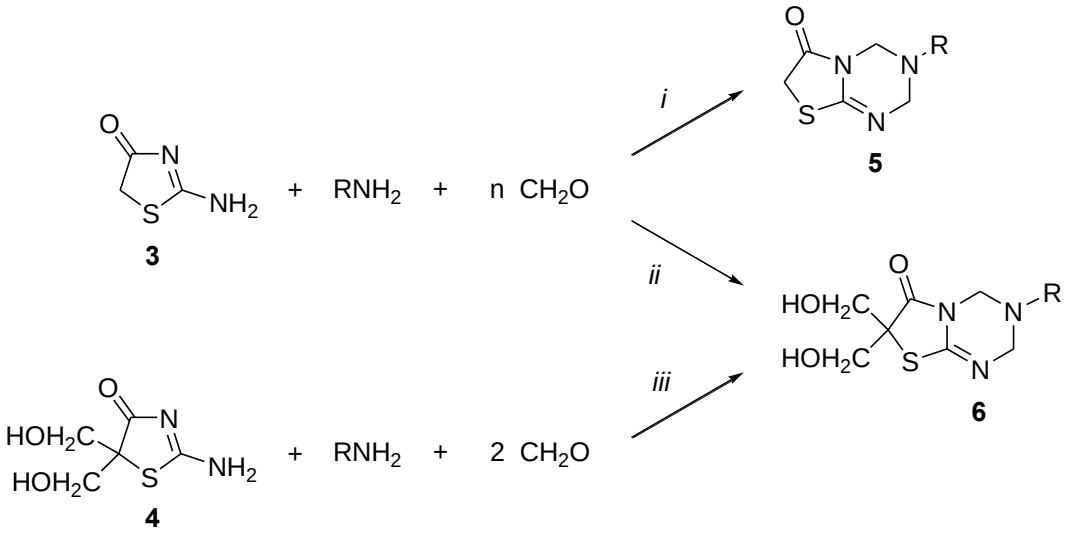
2.1.1. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines using Mannich condensation.

The Mannich reaction of 2-aminothiazolin-4-one (**3**) and its 5-substituted derivatives with formaldehyde and variety of amines was extensively explored. The substitution at position 5 of 2-aminothiazolin-4-one (**3**) and nature of the amine used in the reaction were found to determine structure of the product. Thus, reaction of **3** with formaldehyde and methylamine or aromatic amines resulted in the formation of Mannich bases **5** (Scheme 2).[4,5]

However, when *t*-buthylamine or benzylamine were used in this reaction, hydroxymethylation at position 5 of **3** took place together with 1,3,5-triazine ring closure providing **6c** and **6e**.[6] Additionally, spiro-fused compound **7** was isolated from the reaction of **3** with formaldehyde and *t*-buthylamine. The hydrolysis of **6c** and **7** was investigated in details by Ramsh *et al*.[7] The aminomethylation of amidine moiety of **4** afforded 3-alkyl and 3-aralkyl substituted **6** (Scheme 2).[8] Compounds of this type, *e.g.* **6d** were among leads for the development of agents selectively targeting Fanconi anemia pathway-deficient tumors.[9]

The pathway of the reaction of 5-alkyl substituted 2-aminothiazolin-4-ones (**8**) with formaldehyde and amines was found to depend on the amine structure and the substitution at position 5 of **8**. In the reaction with β-naphthylamine, the products of the aminomethylation (**9**) were obtained exclusively, while their

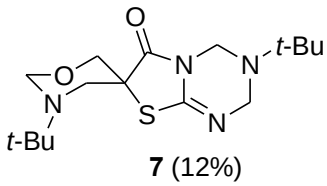
hydroxymethylated analogues (**10**) were formed using *t*-buthylamine (Scheme 3).[4,6,8] The reaction of methyl and ethyl substituted **8** with formaldehyde and aniline provided **10b** and **9b**, respectively.[6]



i: R = Me, 65% (**5a**); Ph, 89% (**5b**); 3-ClC_6H_4, 90% (**5c**); 3-BrC_6H_4, 88% (**5d**); 3-$NO_2C_6H_4$, 42% (**5e**); 3-MeC_6H_4, 84% (**5f**); 4-MeC_6H_4, 89% (**5g**); 4-$MeOC_6H_4$, 90% (**5h**); 2-Naphth, 89% (**5i**)

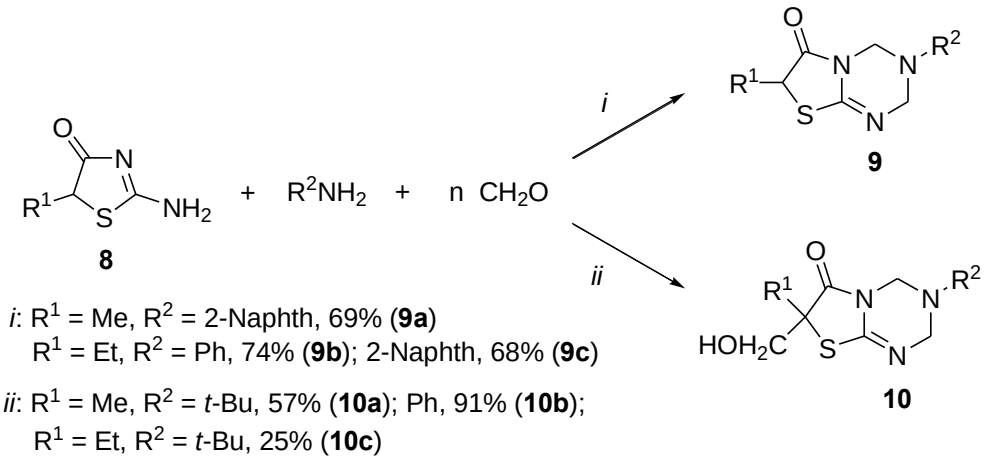
ii: R = *t*-Bu, 22% (**6c**); Bn, 28% (**6e**)

iii: R = Me, 71% (**6a**); Et, 40% (**6b**), *t*-Bu, 70% (**6c**); *c*-Hex, 76% (**6d**); Bn, 46% (**6e**); $CHPh_2$, 98% (**6f**)



7 (12%)

Scheme 2

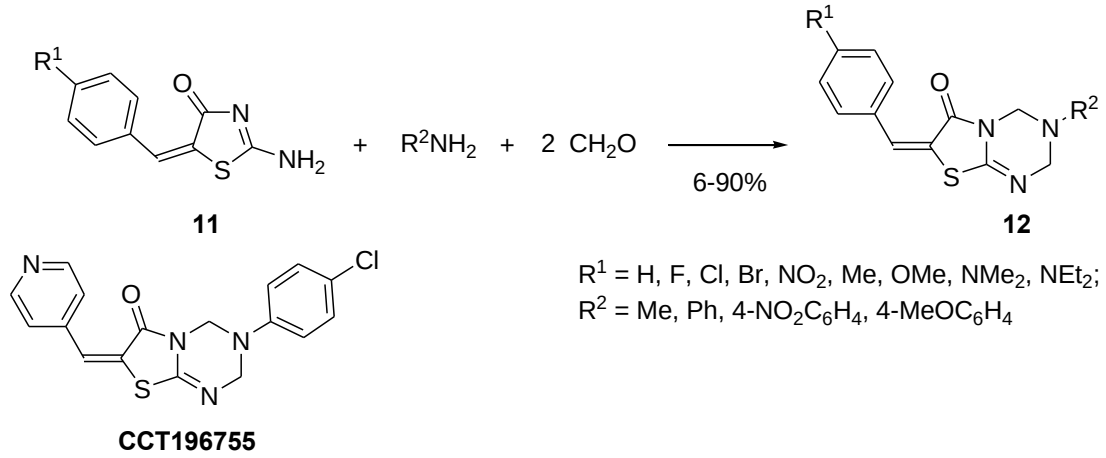


i: R^1 = Me, R^2 = 2-Naphth, 69% (**9a**)
R^1 = Et, R^2 = Ph, 74% (**9b**); 2-Naphth, 68% (**9c**)

ii: R^1 = Me, R^2 = *t*-Bu, 57% (**10a**); Ph, 91% (**10b**);
R^1 = Et, R^2 = *t*-Bu, 25% (**10c**)

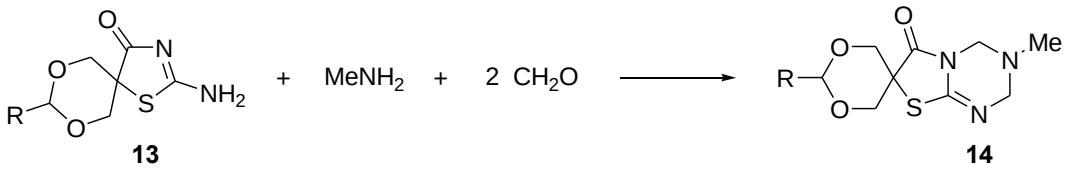
Scheme 3

Similar reaction of 5-arylidene substituted 2-aminothiazolin-4-ones (**11**) was used for the preparation of a series of corresponding Mannich bases **12** (Scheme 4).[4,6,10] One of this type of compounds, CCT196755, was identified as an inhibitor of phospholipase C-γ with IC_{50} = 15 μM in the functional cell based assay.[11]



Scheme 4

Analogously, **13** reacted with formaldehyde and methylamine to produce **14** (Scheme 5).[8] These compounds were also found to be potential agents against Fanconi anemia pathway-deficient tumors.[9]



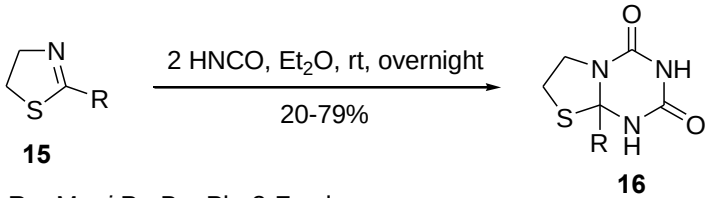
R = Ph, 83% (**14a**); 4-$NO_2C_6H_4$, 77% (**14b**); 4-MeC_6H_4, 75% (**14c**); 3-Py, 50% (**14d**); 4-Py, 46% (**14e**)

Scheme 5

2.1.2. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines using multicomponent reactions of thiazole derivatives with heterocumulenes.

The pathways of multicomponent reactions of thiazoles with heterocumulenes were found to involve the cycloaddition, which may be accompanied by other processes depending on structure of the substrate and reaction conditions. The most common heterocumulenes used in the reaction were isocyanates.

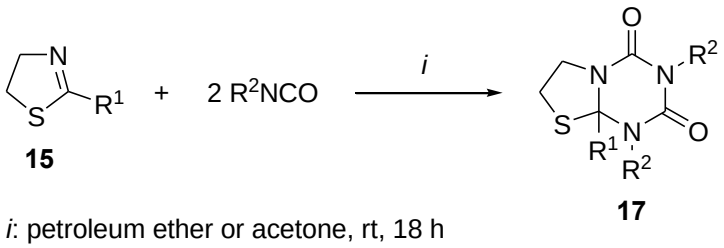
Several cycloaddition reactions of 2-substituted thiazolines with isocyanic acid and its derivatives were used for the synthesis of thiazolo[3,2-*a*][1,3,5]triazin-2,4-diones. Thus, the reaction of thiazolines **15** with two molecules of isocyanic acid resulted in the annelation of 2,4-dioxotriazine ring affording **16** (Scheme 6).[12] In the biological screening, **16** showed activity against Walker's carcinoma 256 when tested in rats.



R = Me, *i*-Pr, Bn, Ph, 2-Furyl

Scheme 6

In a similar way, adducts **17** were formed upon treatment of **15** with aryl isocyanates (Scheme 7).[13]

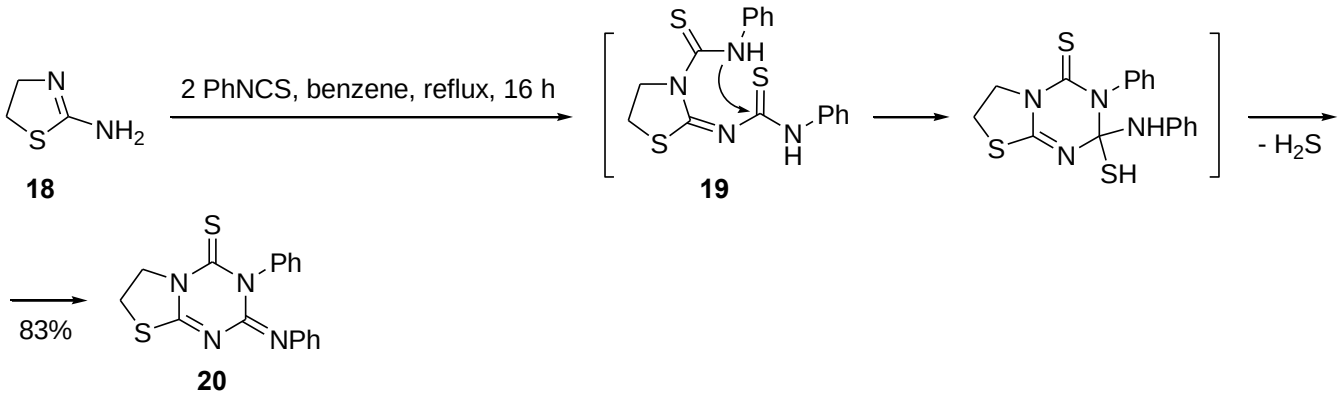


i: petroleum ether or acetone, rt, 18 h
R^1 = *N*-pyrrolidinyl, R^2 = 4-ClC_6H_4, 86% (**17a**), 1-Naphth, 87% (**17b**);

i: 100 °C, 5 h
R^1 = *N*-morpholinyl, R^2 = 1-Naphth, 42% (**17c**)

Scheme 7

2-Aminothiazoline (**18**) reacted with excess of phenyl isothiocyanate affording thiazolo[3,2-*a*][1,3,5]triazine **20**, which was rationalized to form *via* the triazine ring closure of intermediate 1:2 adduct **19** with subsequent elimination of hydrogen sulfide (Scheme 8).[14] The structure of **20** was unequivocally established using X-ray crystallography.[15] An attempt to obtain similar product using 1-naphthyl isothiocyanate instead of phenyl isothiocyanate was unsuccessful.

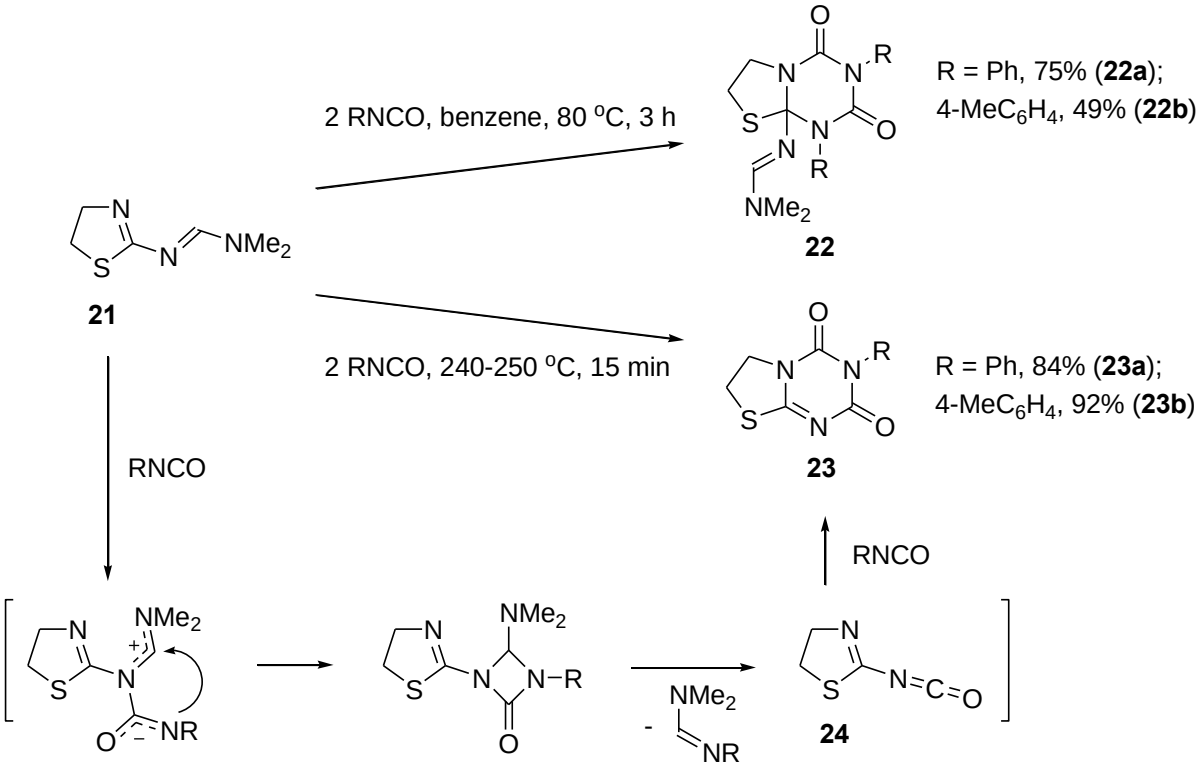


Scheme 8

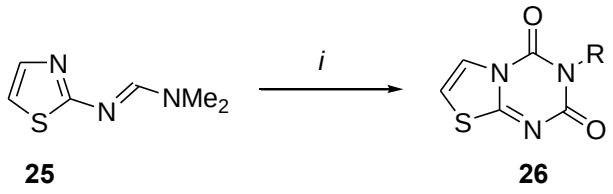
Another thiazoline derivative, formamidine **21**, reacted with aryl isocyanates in mild conditions *via* the [4+2] cycloaddition (*vide infra* Scheme 58).[16] However, heating **21** with excess of aryl isocyanates in benzene afforded 1:2 adduct **22** (Scheme 9).[16] Using higher temperature and excess of aryl isocyanates resulted in the formation of **23**. In this case, the synthetic pathway might be rationalized by [4+2] cycloaddition of presumable intermediate - thiazolin-2-yl isocyanate (**24**) and aryl isocyanate molecule.

It was shown in the same work,[16] that formamidine **25** reacted with aryl isocyanates affording the formation of 3-arylthiazolo[3,2-*a*][1,3,5]triazin-2,4-diones (**26**) in all of the reaction conditions applied (Scheme 10).

Similarly, benzofused analogues **28** were obtained from **27** and aryl isocyanates (Scheme 11).[16]

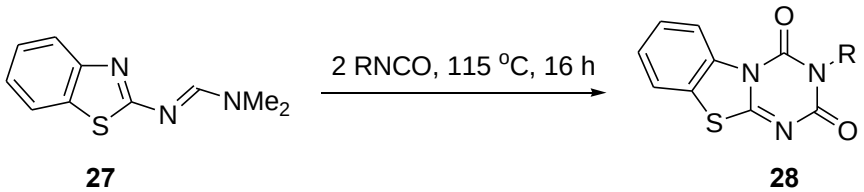


Scheme 9



i: 2 PhNCO, Et_2O, 20 °C, 16 h
R = Ph, 65% (**26a**);
i: 2 4-MeC_6H_4NCO, benzene, 80 °C, 1 h
R = 4-MeC_6H_4, 54% (**26b**)

Scheme 10

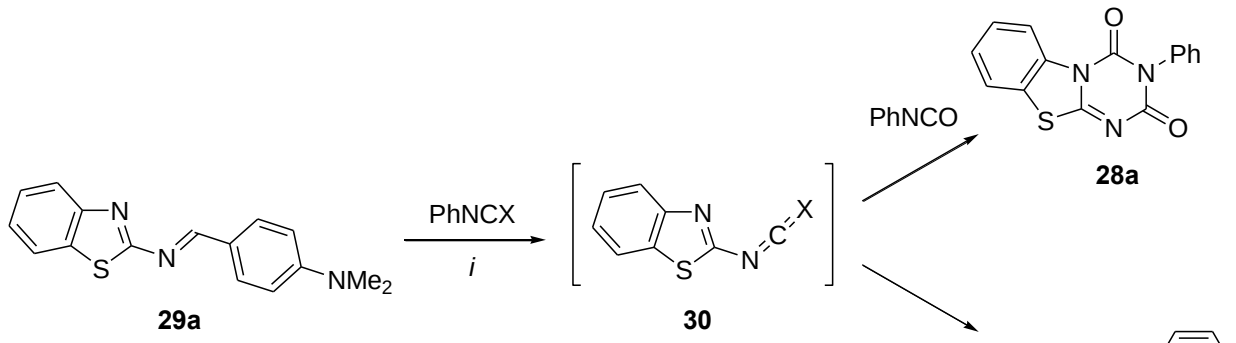


R = Ph, 56% (**28a**); 3-MeC_6H_4, 90% (**28b**)

Scheme 11

Instead of expected [4+2] cycloaddition (*vide infra* Scheme 60), heating 2-(4-dimethylaminobenzylidenamino)benzothiazole (**29a**) with phenyl isocyanate or phenyl

isothiocyanate in inert solvent resulted in the formation of the corresponding 2-benzothiazolyl isocyanate or 2-benzothiazolyl isothiocyanate (**30**) (Scheme 12).[17] In case of the excess of phenyl isocyanate, the cycloaddition afforded **28a**. If no excess of phenyl isocyanate was available, 2-benzothiazolyl isocyanate as well as its thio-analogue (**30**) dimerized to **31** (Scheme 12). The electronodonor properties of the dimethylamino group were proposed to be responsible for the reaction pathway. However, the basicity of this group seems to be a more important factor determining the product structure.

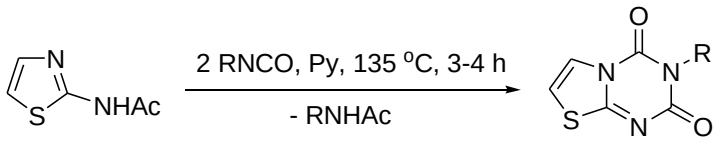


i: PhNCO (2 eq.), toluene, reflux, 16 h - **28a** (60%)
PhNCX (1 eq.), benzene, reflux, 50-70 h - **31** (55%)

X = O (**31a**), S (**31b**)

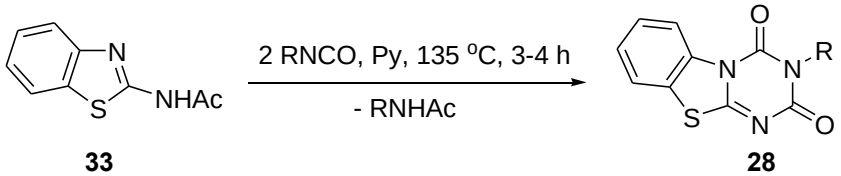
Scheme 12

3-Arylthiazolo[3,2-*a*][1,3,5]triazin-2,4-diones (**26** and **28**) were also prepared by heating corresponding acetamides **32** and **33** with aryl isocyanates in pyridine (Schemes 13 and 14).[18]



R = Ph, 53% (**26a**); 4-ClC_6H_4, 84.5% (**26c**); 3,4-$Cl_2C_6H_4$, 63% (**26d**)

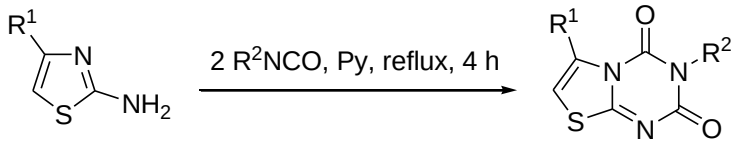
Scheme 13



R = Ph, 75% (**28a**); 3-ClC_6H_4, 87% (**28c**); 4-ClC_6H_4, 90% (**28d**);
4-$NO_2C_6H_4$, 87% (**28e**); 3,4-$Cl_2C_6H_4$, 92% (**28f**)

Scheme 14

2-Aminothiazole **34** was reported[19] to react with aryl isocyanates in pyridine affording the formation of 3-arylthiazolo[3,2-*a*][1,3,5]triazin-2,4-diones (**35**) (Scheme 15).

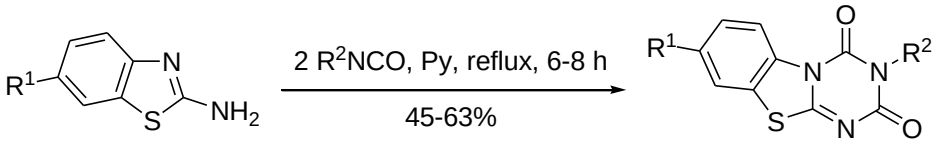


34 **35**

R^1 = 2-benzimidazolyl, R^2 = Ph, 36% (**35a**); 2-$MeOC_6H_4$, 25% (**35b**)

Scheme 15

Benzofused analogues **37** were synthesized from 2-aminobenzothiazoles (**36**) (Scheme 16).[20] The compounds **37** underwent biological screening against *Mycobacterium tuberculosis* $H_{37}RV$. The most active compound (**37**, R^1 = OEt, R^2 = Ph) showed inhibition of *M. tuberculosis* at 0.12 μg/ml.

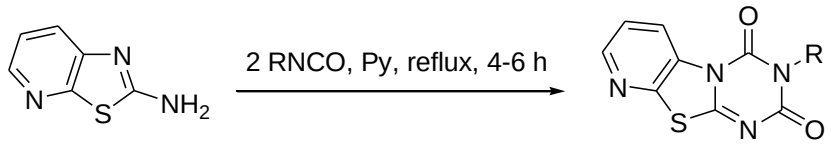


36 **37**

R^1 = Cl, Br, OMe, OEt, OPr; R^2 = *n*-Bu, Ph, 2-$MeOC_6H_4$

Scheme 16

Another series of tricyclic thiazolo[3,2-*a*][1,3,5]triazines (**39**), which possessed anthelmintic activity against *Nematospiroides dubius*, was prepared from amines **38** using similar method (Scheme 17).[19]



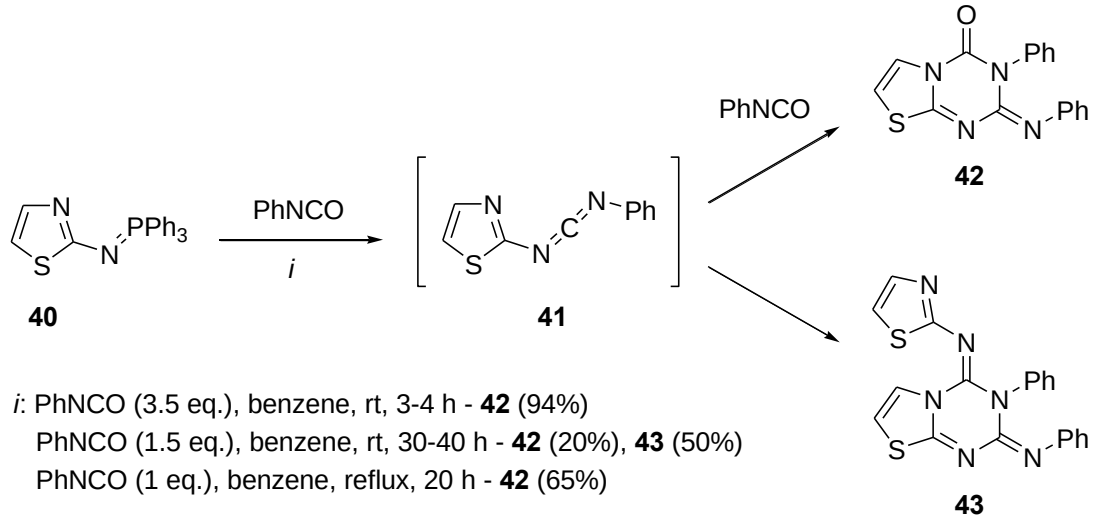
38 **39**

R = Ph, 55% (**39a**); 2-ClC_6H_4, 40% (**39b**); 2-$MeOC_6H_4$, 40% (**39c**); 2-$EtOC_6H_4$, 35% (**39d**)

Scheme 17

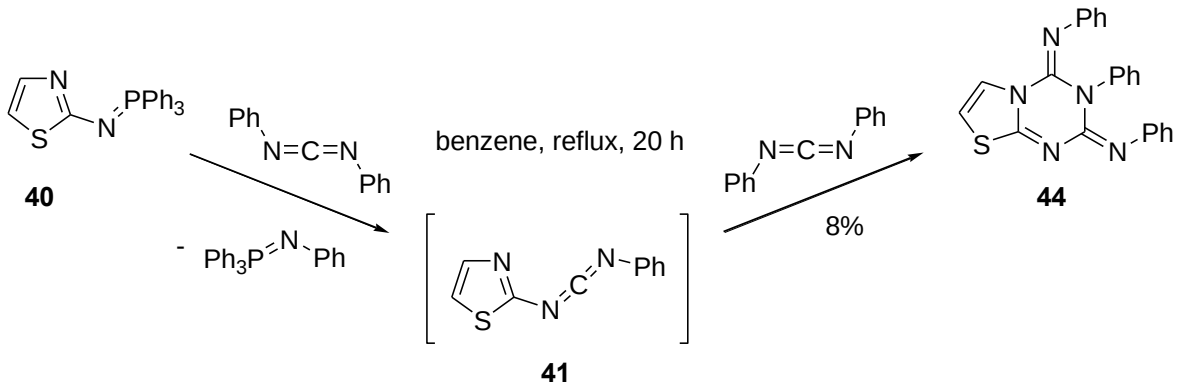
The reactions of 2-thiazolyliminotriphenylphosphorane (**40**) with various heterocumulenes were studied in details by Bödeker *et al.*[21,22] Phenyl isocyanate was found to react with **40** affording two thiazolo[3,2-*a*][1,3,5]triazines **42** and **43** (Scheme 18).[21] The formation of both products was suggested to proceed *via* intermediate carbodiimide **41**, which depending on the reaction condition undergoes either [4+2] cycloaddition with another molecule of phenyl isocyanate providing **42** or dimerization to **43**.

Using excess of phenyl isocyanate and mild reaction conditions allowed preparation of **42** in good yield, whereas prolonged heating equimolar quantities of **40** and phenyl isocyanate resulted in the isolation of **43**, exclusively.



Scheme 18

The reaction of **40** with diphenylcarbodiimide provided **44** (Scheme 19).[22] The proposed mechanism involved the initial formation of intermediate **41** followed by the cycloaddition of another diphenylcarbodiimide molecule. The low yield of **44** was associated with the polymerization observed during the reaction.

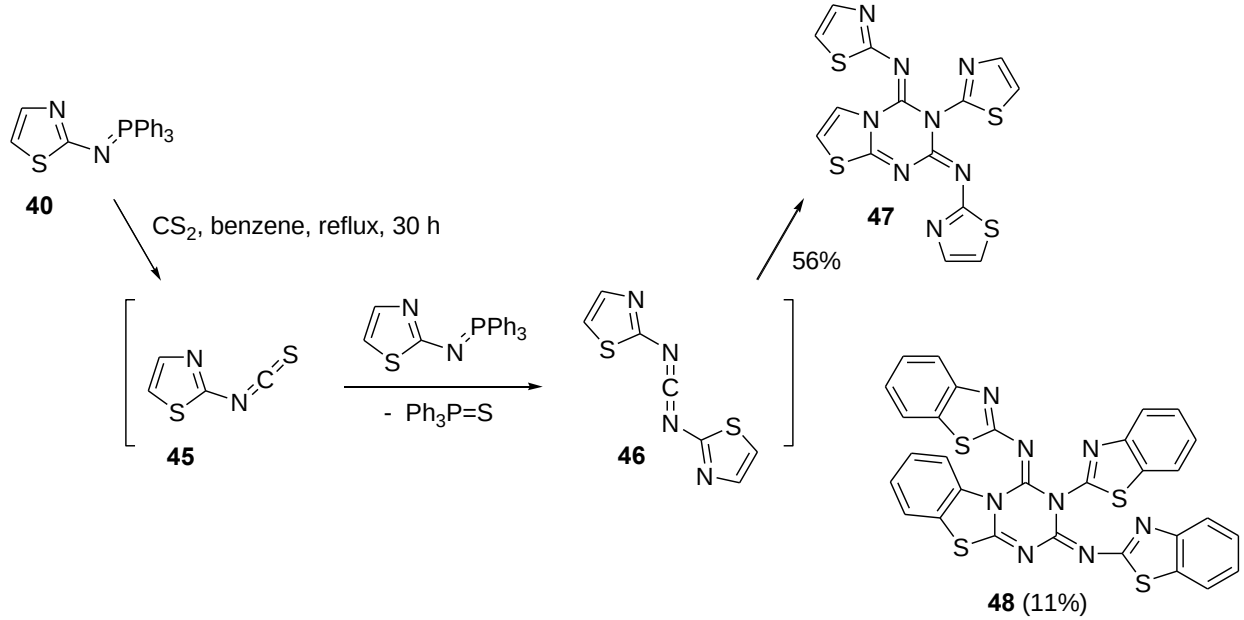


Scheme 19

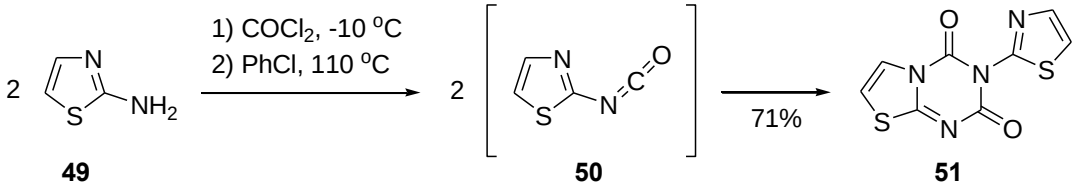
The treatment of 2-thiazolyliminotriphenylphosphorane (**40**) with carbon disulfide afforded the formation of **47** (Scheme 20).[21] It was proposed that two molecules of **40** and one molecule of carbon disulfide *via* intermediacy of 2-thiazolyl isothiocyanate (**45**) formed di(2-thiazolyl)carbodiimide (**46**), which underwent subsequent dimerization providing **47**. Similarly, benzofused analogue **48** was also prepared, but with lower yield.

2.1.3. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines using other multicomponent reactions of 2-aminothiazoles and their derivatives.

The pseudo-four-component reaction of 2-aminothiazole (**49**) with phosgene afforded 3-(2-thiazolyl)thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**51**) (Scheme 21).[23] The mechanism of the reaction was based on the dimerization of *in situ* formed 2-thiazolyl isocyanate (**50**). Analogous benzofused dimer **31a** was prepared in the same way with the 21% yield (*cf.* Scheme 12).

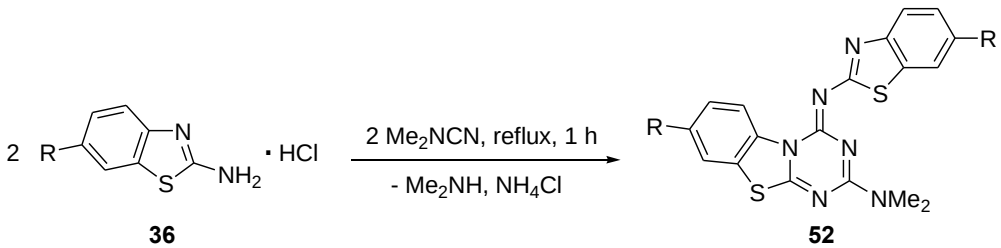


Scheme 20



Scheme 21

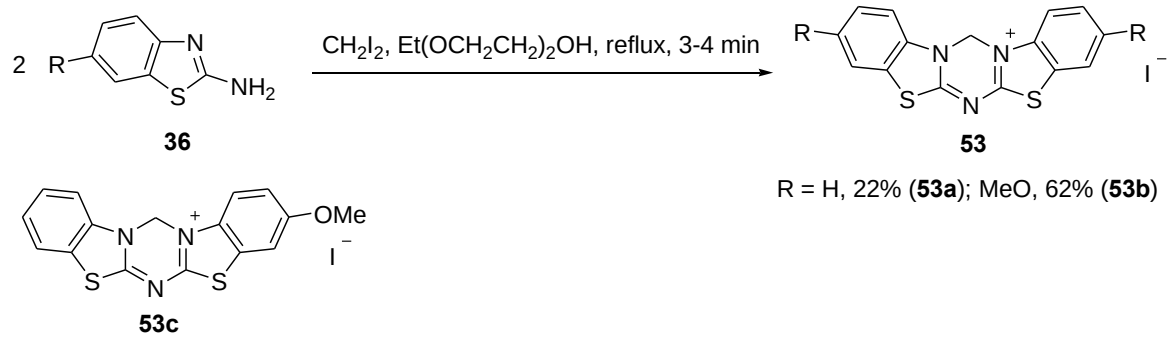
When 2-aminobenzothiazoles (**36**) were heated with excess of dimethylcyanamide, fused triazines **52** were formed instead of expected guanidines (Scheme 22).[24] Two molecules of **36** and two molecules of dimethylcyanamide are involved in the condensation.



R = H, 50% (**52a**); Br, 29% (**52b**)

Scheme 22

Benzothiazoazacyanines (*bis*-benzothiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazin-12-ium iodides) **53** were conveniently prepared from 2-aminobenzothiazoles (**36**) by the reaction with diiodomethane at high temperature (Scheme 23).[25,26] Recently, the binding of **53** to a variety of nucleic acid sequences was investigated. With poor affinity to the duplex DNA strands, compounds **53** exhibited tight binding to G-quadruplex[27] and poly(A).[28]



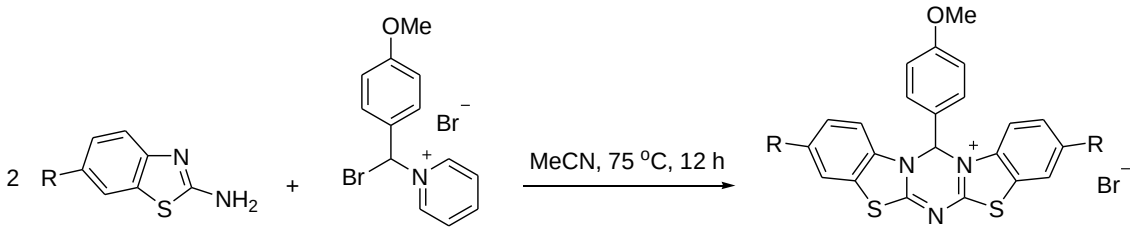
36 **53**

R = H, 22% (**53a**); MeO, 62% (**53b**)

53c

Scheme 23

13-(4-Methoxyphenyl)-13*H*-*bis*-benzothiazolo[3,2-*a*:3',2'-*d*][1,3,5]triazin-12-ium bromides (**55**), structurally related to **53**, were synthesized by treatment of 2-aminobenzothiazoles (**36**) with **54** (Scheme 24).[29] When equimolar mixture of **36** with R = Me and R = MeO was used in the reaction, the product with unsymmetrical substitution was isolated in the yield of 22% together with about 10% of each symmetrical compounds **55b** and **55c**.



36 **54** **55**

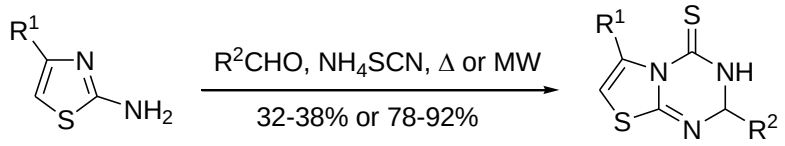
R = H, 43% (**55a**); Me, 37% (**55b**); MeO, 39% (**55c**)

Scheme 24

The three-component solvent-free reaction of 2-amino-4-arylthiazoles (**56**) with aromatic aldehydes and ammonium thiocyanate was reported[30] to afford thiazolo[3,2-*a*][1,3,5]triazines **57** (Scheme 25). Using microwave irradiation substantially improved yields of **57** and shortened the reaction time. The products (**57**) were further effectively glycosylated at N-3.

Another three-component solvent-free synthesis of thiazolo[3,2-*a*][1,3,5]triazines **59** was performed using thiazole Schiff bases **58**, ammonium acetate and aromatic aldehydes (Scheme 26).[31] This methodology

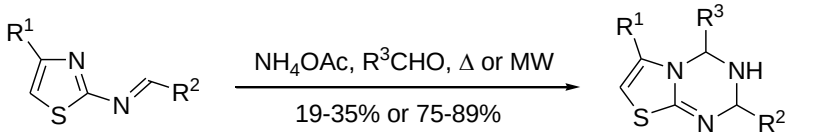
was also extended to *C*-nucleosides **59** by application of aldoses instead of benzaldehydes.[32] In all cases, microwave irradiation was more efficient than conventional heating due to shorter reaction time and higher yields of **59**. Moreover, under the microwave irradiation conditions, the reaction diastereoselectivity was dramatically improved from 51-60% to 93-99%.



56 **57**

R^1 = Ph, 4-MeC_6H_4; R^2 = Ph, 4-$MeOC_6H_4$

Scheme 25



58 **59**

R^1 = Ph, 4-MeC_6H_4; R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4;
R^3 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, D-arabinobutyl, D-ribobutyl, D-glucopentyl

Scheme 26

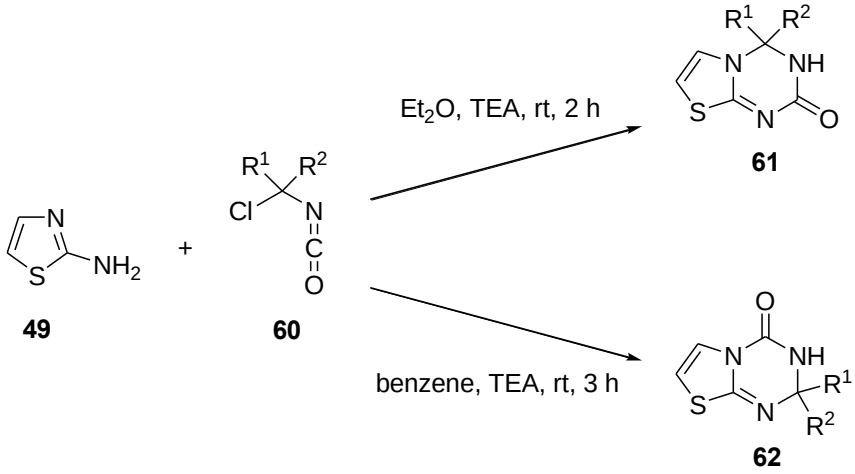
2.1.4. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines *via* reactions of 2-aminothiazoles with C-N-C triatomic synthons.

The large number of readily available 2-aminothiazoles makes them popular as building blocks for the construction of thiazolo[3,2-*a*][1,3,5]triazines. A variety of the -C-N-C- triatomic synthons were applied to build properly substituted 1,3,5-triazine ring on the 2-aminothiazole scaffold. However, regiochemistry of the ring closure was not always discussed and the structure assignments were often uncertain.

The isocyanates and their analogues, bearing at the nitrogen atom another reactive electrophilic group, represent one type of the commonly used -C-N-C- triatomic synthons. The nature of the electrophilic group attached to the isocyanate determines the substitution on the triazine ring as well as affects the regioselectivity of the reaction.

Two alternative pathways are possible for the reactions of isocyanates with 2-aminothiazoles depending on the site of electrophilic attack of the isocyanate group. The reaction of 2-aminothiazole (**49**) with isocyanates **60** in the presence of base might theoretically proceed *via* addition of isocyanate group to exo- or endocyclic nitrogen atom thus resulting in the formation of two regioisomeric products **61** and **62**, respectively (Scheme 27). Initially, this reaction was reported[33,34] to afford 3,4-dihydrothiazolo[3,2-*a*]-

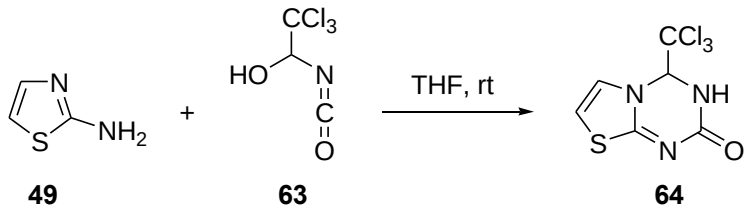
[1,3,5]triazin-2-ones (**61**), but no evidence were provided in support of the product identity. Later, structure **62** was assigned for the products of similar reactions on the basis of the chemical shift of the CF_3 signal in the ^{19}F NMR spectra.[35] These data also seem to be insufficient for unambiguous structure assignments.



R^1= Ph, R^2 = $CHCl_2$, 71% (**61a**); CCl_3, 70% (**61b**)
R^1= Ph, R^2 = CF_3, 72% (**62a**); *t*-Bu, 64% (**62b**); R^1 = 4-MeC_6H_4, R^2 = CF_3, 59% (**62c**)

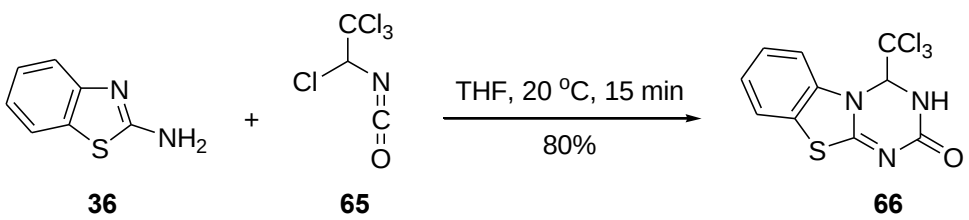
Scheme 27

The product of the reaction of 2-aminothiazole (**49**) with l-hydroxy-2,2,2-trichloroethyl isocyanate (**63**) was reported[36] as similar to **61** 4-trichloromethyl-3,4-dihydrothiazolo[3,2-*a*][1,3,5]triazin-2-one (**64**) (Scheme 28). The regioisomeric structure was not discussed. The hydroxyl of **63** acted as a leaving group instead of chloride in **60**.



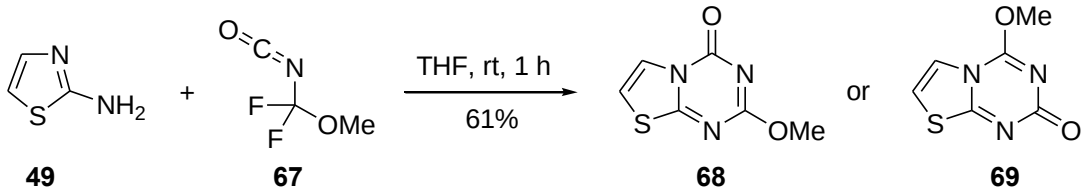
Scheme 28

The benzofused analogue of **64** – tricyclic structure **66** was obtained from 2-aminobenzothiazole (**36**) and l,2,2,2-tetrachloroethyl isocyanate (**65**) (Scheme 29).[37]



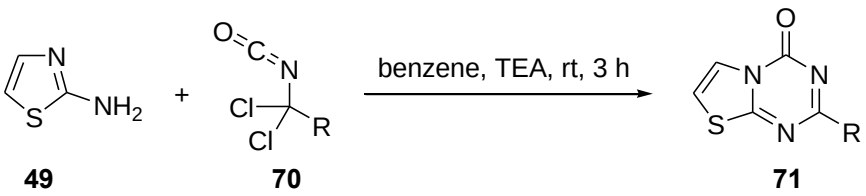
Scheme 29

Two isomeric structures 2-methoxythiazolo[3,2-*a*][1,3,5]triazin-4-one (**68**) and 2-methoxy-thiazolo[3,2-*a*][1,3,5]triazin-4-one (**69**) were proposed for the product of the reaction of 2-aminothiazole (**49**) with methoxydifluoromethyl isocyanate (**67**) (Scheme 30).[38]



Scheme 30

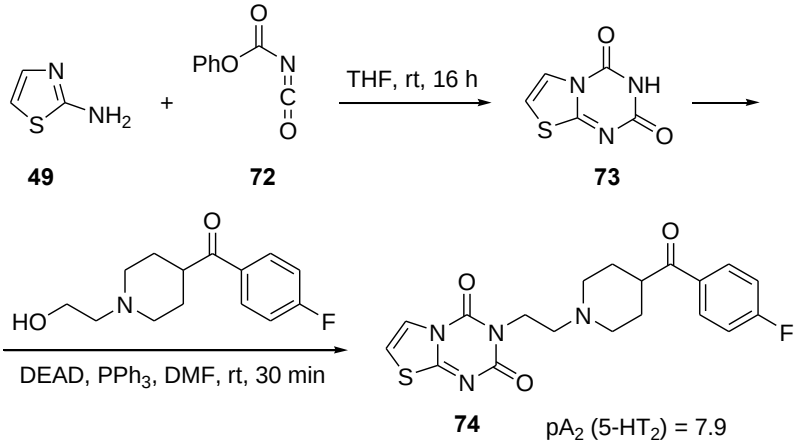
The chemical shift of the CF_3 signal in the ^{19}F NMR spectra was used as an evidence supporting formation of thiazolo[3,2-*a*][1,3,5]triazin-4-ones **71** in similar reaction of **49** with 1,1-dichloro substituted alkyl isocyanates (**70**) (Scheme 31).[35]



R = CF_3, 81% (**71a**); CCl_3, 84% (**71b**)

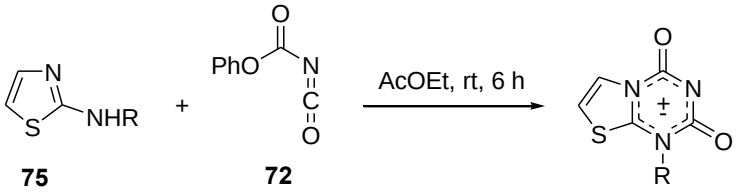
Scheme 31

The reaction of 2-aminothiazole (**49**) with phenoxycarbonyl isocyanate (**72**) was reported[39,40] to produce thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**73**), which was used for the preparation of potent 5-HT_2-receptor antagonists, *e.g.* **74** (Scheme 32).[39-41]



Scheme 32

2-Aminothiazoles with alkylated amino group (**75**) reacted with **72** affording mesoionic thiazolo[3,2-*a*][1,3,5]triazin-2,4-diones **76** (Scheme 33).[42]

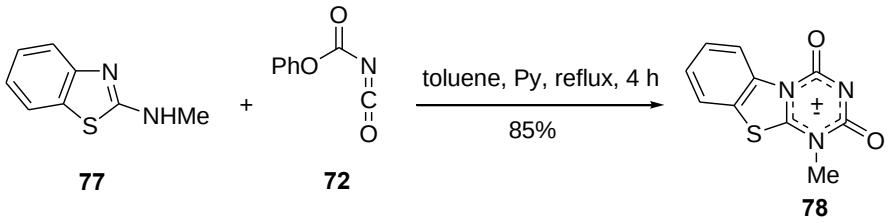


75 **72** **76**

R = Et, 51% (**76a**); Bn, 32% (**76b**)

Scheme 33

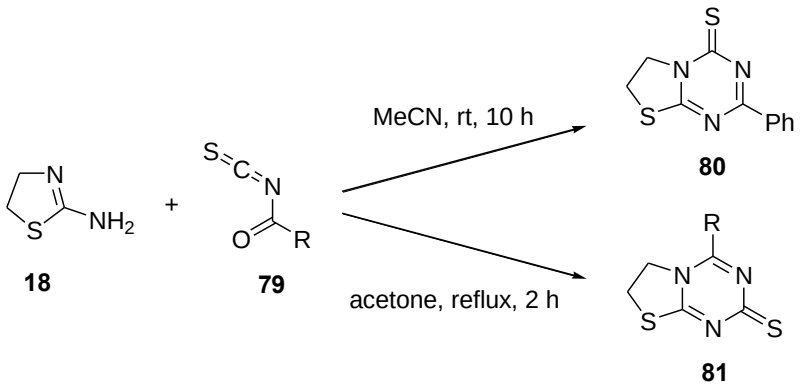
Gotthardt and Blum[43] reported the synthesis of benzofused mesoionic thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione **78** by treatment of amine **77** with phenoxycarbonyl isocyanate (**72**) (Scheme 34). The reactivity of **78** was also investigated.



77 **72** **78**

Scheme 34

Two alternative pathways were reported for the reactions of *N*-benzoyl isothiocyanate (**79**, R = Ph) with 2-aminothiazoline (**18**) (Scheme 35). Klayman and Woods[44] obtained **80** and confirmed the regiochemistry of the reaction by spectral data and chemical properties of the product. Together with **80** (10%), two other products *i.e.* *N*-benzoyl-*N'*-(2-thiazolin-2-yl)thiourea (28%) and thiocyanate of 2-benzamido-2-thiazoline (14%) were isolated from the reaction. Later, another structure **81** was assigned for the product of the reaction of **18** with *N*-aroyl isothiocyanates (**79**) formed *in situ* from the corresponding acid chloride and ammonium thiocyanate.[45] The regioisomeric structures **80** were not considered in the paper.[45]

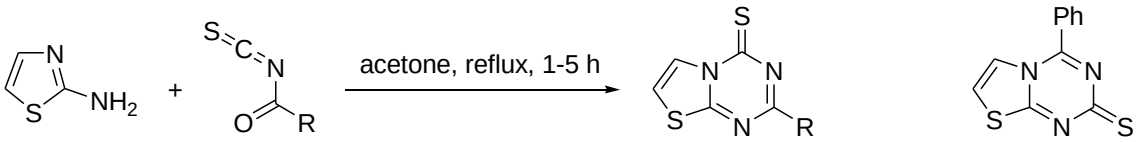


18 **79** **80** **81**

R= Ph, 85% (**81a**); 2-ClC_6H_4, 75% (**81b**); 4-ClC_6H_4, 77% (**81c**); 4-MeC_6H_4, 77% (**81d**); 4-$MeOC_6H_4$, 78% (**81e**); 4-$NO_2C_6H_4$, 78% (**81f**)

Scheme 35

Barnikow and Bödeker [46] explored the reaction of 2-aminothiazole (**49**) with *N*-benzoyl isothiocyanate (**79**) (Scheme 36). They reported formation of 2-phenylthiazolo[3,2-*a*][1,3,5]triazin-4-thione (**82b**) as a main product (22%) together with *N*-benzoyl-*N'*-(2-thiazolyl)thiourea (19%) and 2-benzoylaminothiazole (0.5%). The report[47] on the isolation of regioisomeric 4-phenylthiazolo[3,2-*a*][1,3,5]triazin-2-thione (**83**) seems to be erroneous as the X-ray crystallography data[48] for the similarly obtained product supported the structure of 2-phenylthiazolo[3,2-*a*][1,3,5]triazin-4-thione (**82b**). Analogously, 2-propyl substituted compound **82a** was prepared and its molecular and crystal structure were described.[49] A series of 2-aryl substituted thiazolo[3,2-*a*][1,3,5]triazin-4-thiones (**82**) was synthesized by Saeed *et al.*[50] with surprisingly high yields. The X-ray crystallography data for **82d** were also reported.

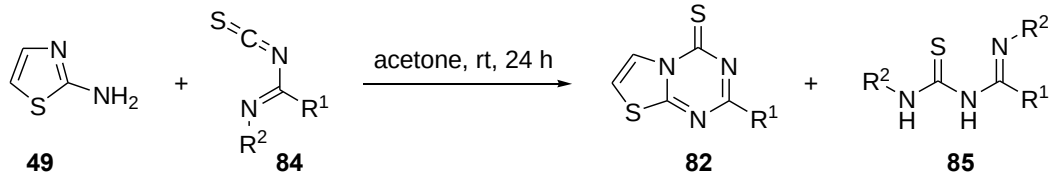


49 **79** **82** **83**

R = Pr (**82a**); Ph, 22% (**82b**); 4-MeC_6H_4, 90% (**82c**); 4-$NO_2C_6H_4$, 93% (**82d**); 2-thienyl, 93% (**82e**)

Scheme 36

N-Aryl benzimidoyl isothiocyanates **84** were reported to react with 2-aminothiazole (**49**) similarly to **79** providing 2-arylthiazolo[3,2-*a*][1,3,5]triazin-4-thiones (**82**) (Scheme 37).[51] The addition of **84** to anilines, formed in the reaction after nucleophilic substitution of the imidoyl group, resulted in the formation of thioureas **85** as side products.

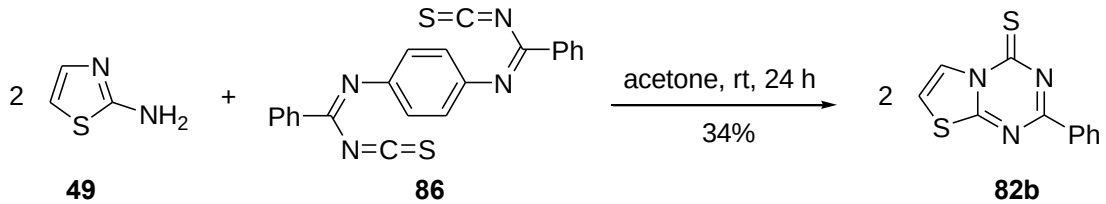


49 **84** **82** **85**

R^1 = Ph, R^2 = Ph, 47% (**82b**) and 42% (**85a**);
R^1 = 4-$NO_2C_6H_4$, R^2 = 4-ClC_6H_4, 48% (**82d**) and 37% (**85b**)

Scheme 37

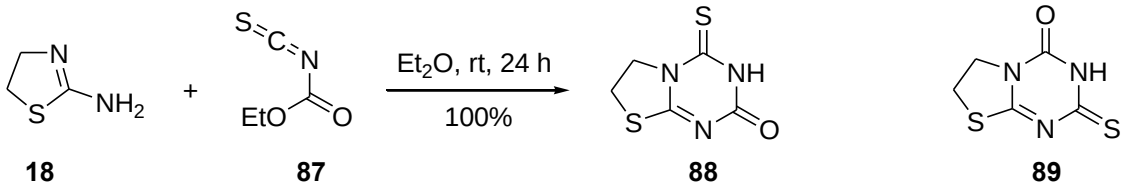
Analogously, 2-phenylthiazolo[3,2-*a*][1,3,5]triazin-4-thione (**82b**) was prepared by treatment of 2-aminothiazole (**49**) with *bis*-imidoyl isothiocyanate **86** (Scheme 38).[52]



49 **86** **82b**

Scheme 38

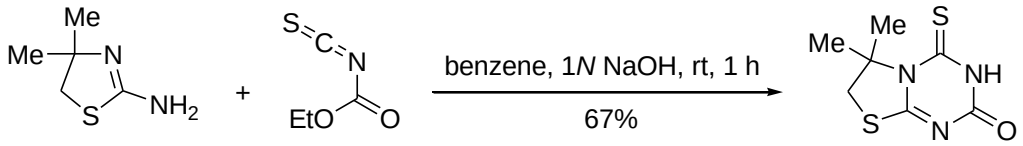
2-Aminothiazoline (**18**) was quantitatively converted to **88** *via* the reaction with ethoxycarbonyl isothiocyanate (**87**) (Scheme 39). Initially, the regioisomeric structure **89** was assigned to the product,[53] but the detail structure investigations by Klayman and Woods[54] and crystallographic information[55] proved that isothiocyanate group of **87** attacked endocyclic nitrogen atom of 2-aminothiazoline (**18**), affording **88** after the triazine ring closure.



18 **87** **88** **89**

Scheme 39

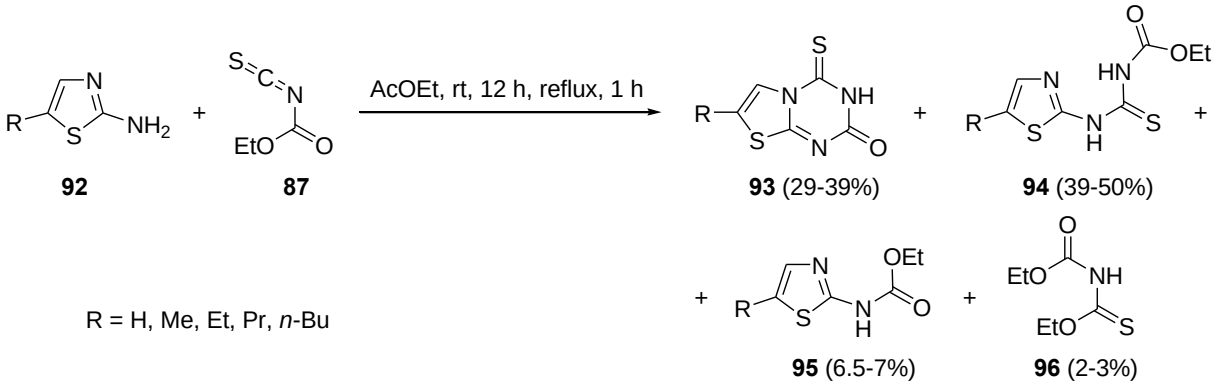
The steric effect of the *gem*-dimethyl substitution at carbon atom adjacent to the endocyclic nitrogen of thiazoline ring was explored.[54] The treatment of 2-amino-4,4-dimethylthiazoline (**90**) with **87** afforded the formation of 4-thioxothiazolo[3,2-*a*][1,3,5]triazin-2-one **91** as a sole regioisomer (Scheme 40). However, presence of the base was required for the reaction to proceed.



90 **87** **91**

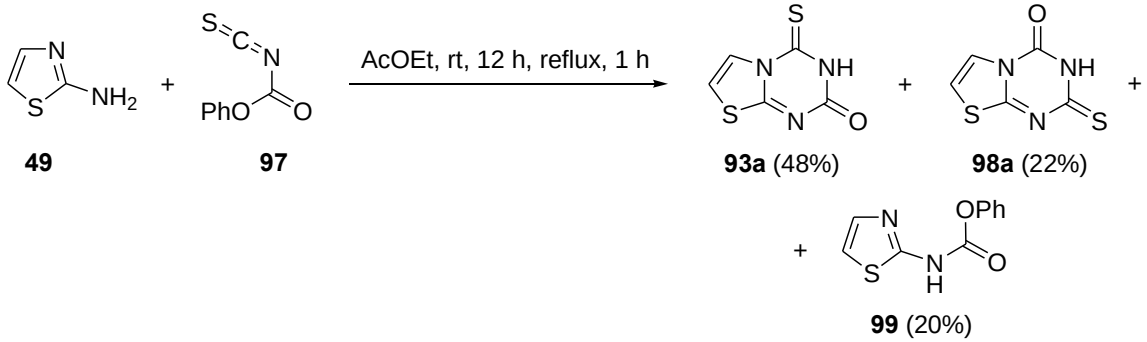
Scheme 40

The reaction of 2-aminothiazoles (**92**) with ethoxycarbonyl isothiocyanate (**87**) was studied in details by Nagano *et al*.[56-58] The effects of substitutions in the thiazole ring on the product yields and composition were explored.[56] The formation of 4-thioxothiazolo[3,2-*a*][1,3,5]triazin-2-ones **93** was observed when 5-substituted 2-aminothiazoles (**92**) with pKa above 5 were treated with **87** (Scheme 41). However, the reaction lacked regioselectivity and was only fairly chemoselective. Together with **93**, three other products, namely *N*-ethoxycarbonyl-*N'*-(2-thiazolyl)thioureas (**94**), *N*-(2-thiazolyl)urethanes (**95**) and *N*-(ethoxythiocarbonyl)urethane (**96**) were isolated from the reaction mixtures. In case of 2-aminothiazoles with the pKa below 5, no thiazolo[3,2-*a*][1,3,5]triazines were isolated from the reaction. Regardless the pKa value, 4-substituted 2-aminothiazoles in the reaction with **87** also did not afford thiazolo[3,2-*a*][1,3,5]triazines. Changing the ethoxy group in **87** to the methoxy one improved yield of **93a** (R = H) from 29% to 41%.[57] The higher alkoxy group (*n*-PrO, *i*-PrO, *n*-BuO and *i*-BuO) decreased yields of **93a** to 19-26%. It was found that on heating, **94a** (R = H) can undergo cyclization to 2-thioxo-thiazolo[3,2-*a*][1,3,5]triazin-4-one (**98**) (*vide infra* Scheme 83).[57] Compounds **93** were claimed as potential bactericides and fungicides for agricultural use.[58]



Scheme 41

Two regioisomeric thiazolo[3,2-*a*][1,3,5]triazines **93a** and **98** were isolated from the reaction of 2-aminothiazole (**49**) with phenoxycarbonyl isothiocyanate (**97**) (Scheme 42).[57] The formation of another side product, phenyl *N*-(2-thiazolyl)carbamate (**99**) was also mentioned.



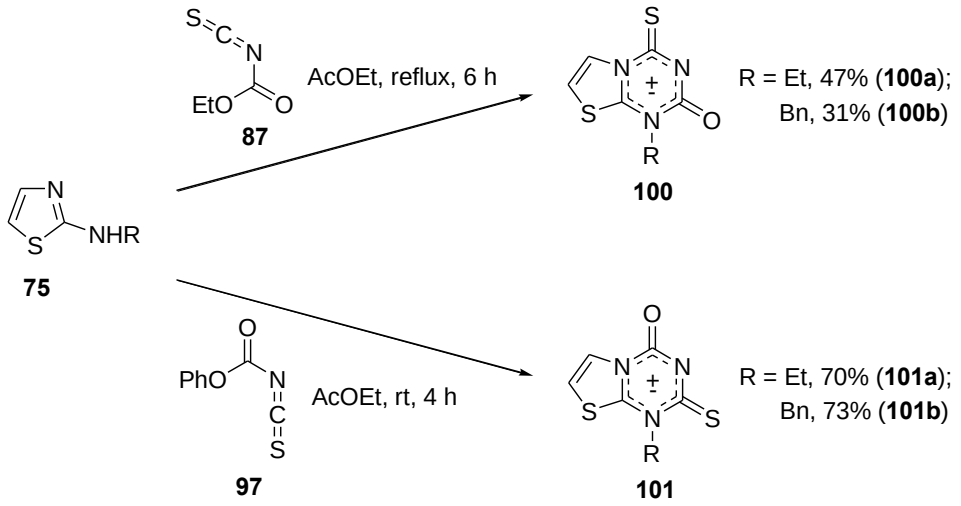
Scheme 42

2-Aminothiazoles with alkylated amino group (**75**) were shown to behave differently in the analogous reactions. The formation of regioisomeric mesoionic thiazolo[3,2-*a*][1,3,5]triazines **100** and **101** was observed when **75** reacted with ethoxycarbonyl isothiocyanate (**87**) and phenoxycarbonyl isothiocyanate (**97**), respectively (Scheme 43).[42] The structures **100** and **101** were assigned on the basis of their further chemical transformations.

2-Arylaminothiazolo[3,2-*a*][1,3,5]triazin-4-thiones (**103**) were synthesized from 2-aminothiazole (**49**) and formamidinoyl isothiocyanates **102** (Scheme 44).[59] The products of the addition of **102** to the amino group of **49**, guanylthioureas **104** were also isolated from the reaction. Using analogues of **102** with piperidino or diethylamino substituents instead of morpholino moiety was reported to give the same products (**103**) of the triazine ring annelation.

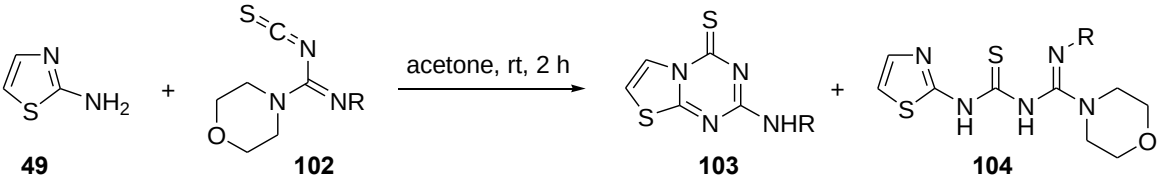
It was reported,[60] that *N*-(1-hydroxyimino-2-oxopropyl)pyridinium chloride (**105**) can be used as a stable and convenient substitute for acetyl isocyanate. The dehydrochlorination of salt **105** provided **106**, which

subsequently rearranged to the active complex of pyridine with acetyl isocyanate (**107**) (Scheme 45). The traces of 2-methylthiazolo[3,2-*a*][1,3,5]triazin-4-one (**108**) were detected in the reaction of **105** with 2-aminothiazole (**49**) in chloroform. Using **49** absorbed on SiO_2 (1:2) allowed isolation of **108** with the 11% yield. Changing the 2-aminothiazole (**49**) – SiO_2 ratio to 1:4 improved yield of 2-methylthiazolo[3,2-*a*][1,3,5]triazin-4-one (**108**) to 22%. Additionally, *N*-acetyl-*N'*-(2-thiazolyl)thiourea (**109**) was isolated from the reaction (Scheme 45).



87 **75** **100** **97** **101**

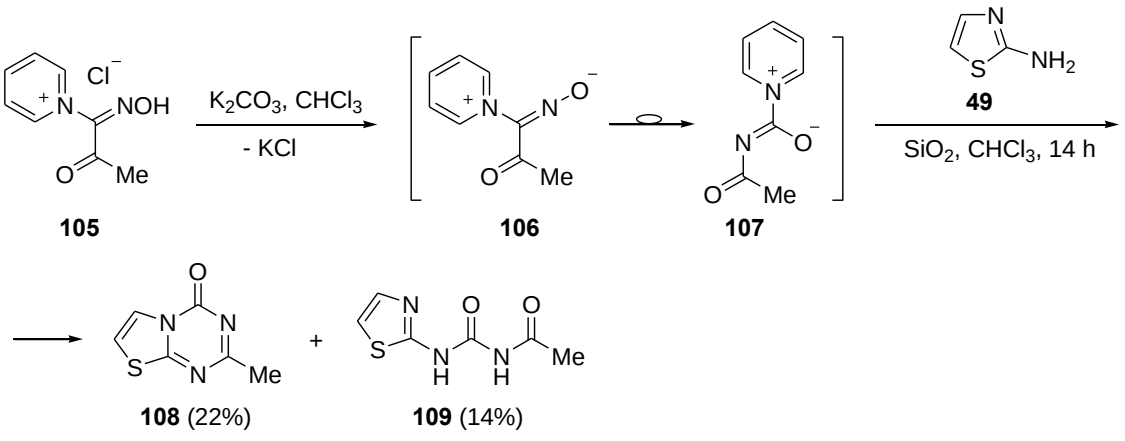
Scheme 43



49 **102** **103** **104**

R = 4-ClC_6H_4, 27% (**103a**), 4-BrC_6H_4, 38% (**103b**), 4-$NO_2C_6H_4$, 37% (**103c**)

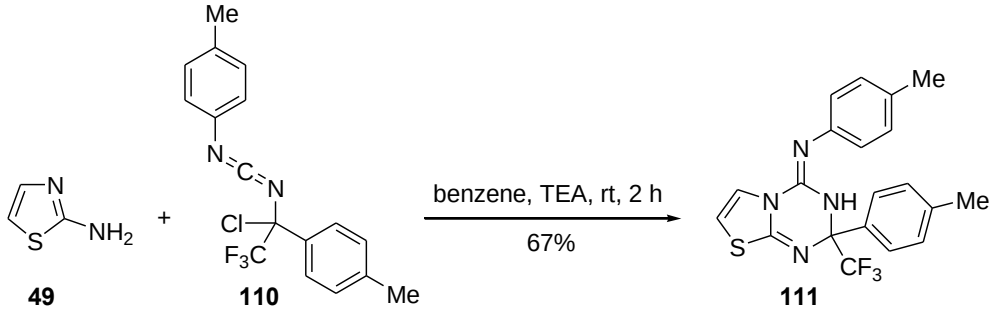
Scheme 44



105 **106** **107** **108** (22%) **109** (14%)

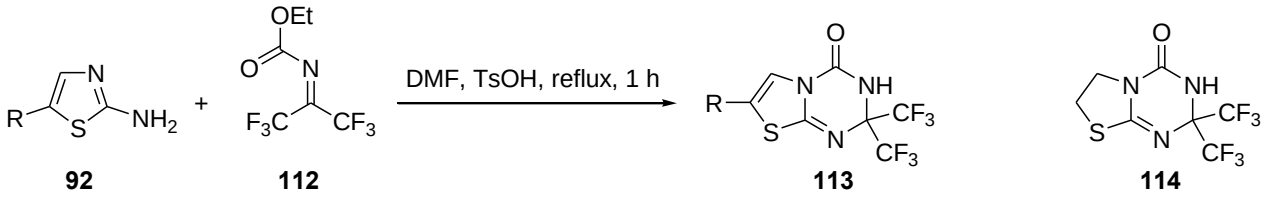
Scheme 45

Vovk and Dorokhov[61] found that reaction of 2-aminothiazole (**49**) with carbodiimide **110**, structurally related to isocyanates **60**, in mild conditions afforded thiazolo[3,2-*a*][1,3,5]triazine **111** with trifluoromethyl group at the quaternary C-2 atom (Scheme 46).



Scheme 46

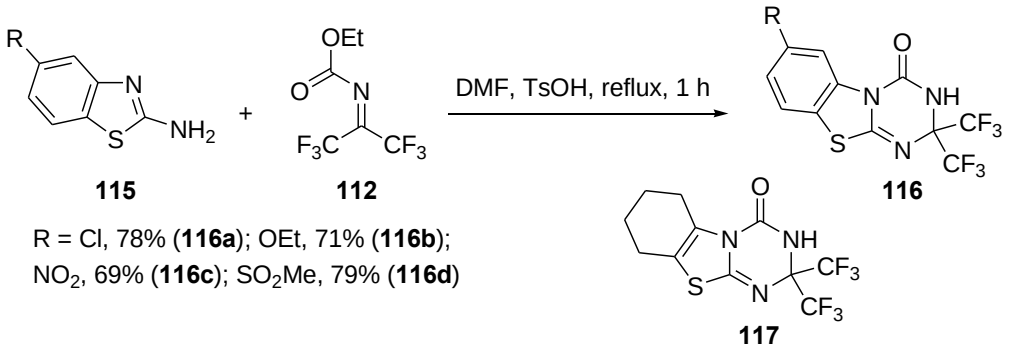
Thiazolo[3,2-*a*][1,3,5]triazin-4-ones **113** (analogues of **62**), substituted with two geminal trifluoromethyl groups, were prepared by treatment of 2-aminothiazoles (**92**) with hexafluoroacetone ethoxycarbonylimine (**112**) in DMF under TsOH catalysis (Scheme 47).[62] The reaction of 2-aminothiazoline (**18**) with imine **112** in the same conditions afforded **114** with the 71% yield.



R = H, 61% (**113a**); Me, 70% (**113b**);
4-$NO_2C_6H_4SO_2$, 76% (**113c**)

Scheme 47

Similarly, benzofused analogues **116** were prepared from 2-aminobenzothiazoles **115** and imine **112** (Scheme 48).[62] Partially saturated **117** was also obtained with the 66% yield using this method.

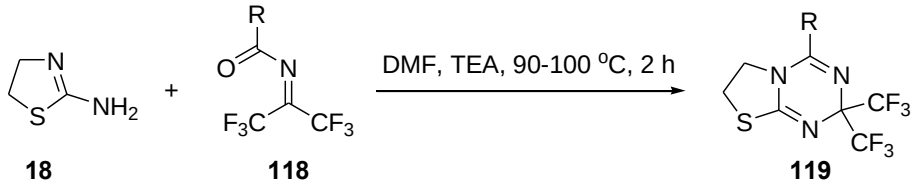


R = Cl, 78% (**116a**); OEt, 71% (**116b**);
NO_2, 69% (**116c**); SO_2Me, 79% (**116d**)

Scheme 48

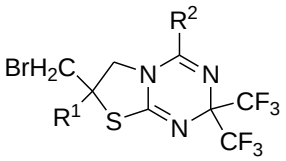
Acylimines of hexafluoroacetone (**118**) were reported[63] to react with 2-aminothiazoline (**18**) with formation of 4-substituted 2,2-bis(trifluoromethyl)-6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazines (**119**)

(Scheme 49). The same reaction was used for the synthesis of **120**.



18 **118** **119**

R = Et, 68% (**119a**); 4-MeC_6H_4, 62% (**119b**); 4-ClC_6H_4, 67% (**119c**); 4-FC_6H_4, 73% (**119d**)

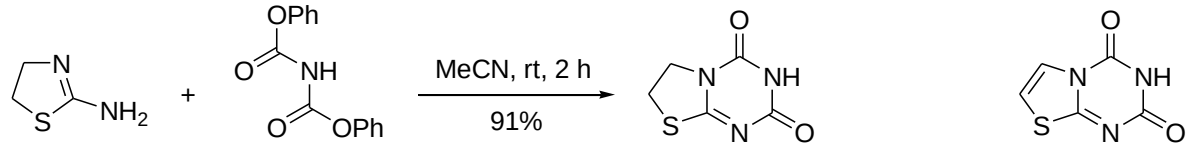


120

R^1 = H, R^2 = Me, 78% (**120a**);
R^1 = Me, R^2 = Ph, 65% (**120b**)

Scheme 49

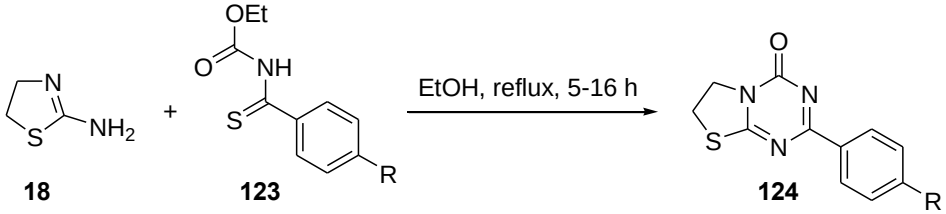
Diphenyl iminodicarboxylate (**121**) was found to be a convenient alternative for relatively unstable phenoxycarbonyl isocyanate (**72**) (*vide supra* Scheme 32). The reaction of 2-aminothiazoline (**18**) with **121** in mild conditions resulted in the formation of 6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**122**) with good yield (Scheme 50).[64] The reaction of 2-aminothiazole (**49**) with **121** required heating in dioxane under reflux for 4.5 h to give thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**73**) with the 75% yield.



18 **121** **122** **73**

Scheme 50

Heating 2-aminothiazoline (**18**) with *N*-ethoxycarbonyl thiobenzamides (**123**) in ethanol was reported[65] to afford 2-aryl-6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4-ones (**124**) (Scheme 51). The conversion of **124a** to its thiocarbonyl analogue **80** was carried out to confirm regioselectivity of the reaction.



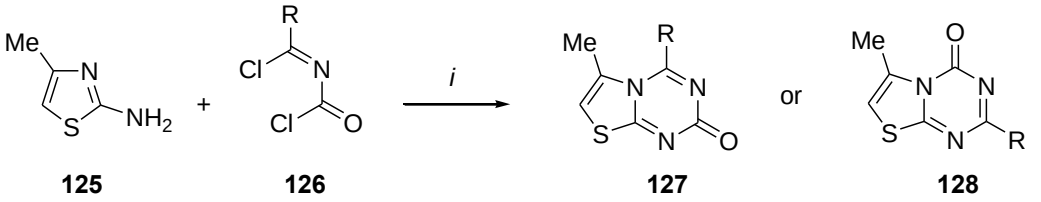
18 **123** **124**

R = H, 78% (**124a**); Me, 69% (**124b**); MeO, 85% (**124c**); EtO, 81% (**124d**)

Scheme 51

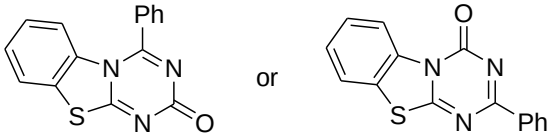
Using carbamoyl chloride **126** was claimed[66] to be effective for the 1,3,5-triazine ring annelation on 2-amino-4-methylthiazole (**125**) (Scheme 52). However, the question on the structure of products (**127** or

128) remained open. Similarly, when 2-aminobenzothiazole (**36**) was reacted with **126** (R = Ph) on heating in diethyl ether for 1 h, either **129** or **130** were proposed as products.



125 **126** **127** **128**

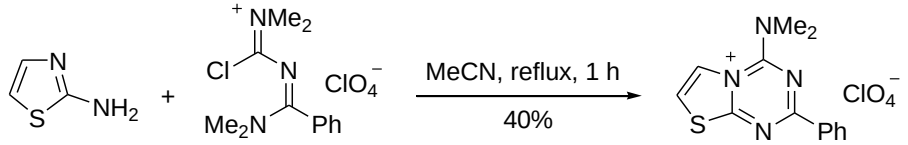
i: Et_2O, 30 min - R = Cl (**127a**/**128a**);
i: dioxane, 70-80 ^oC, 1 h - R = CCl_3 (**127b**/**128b**)



129 **130**

Scheme 52

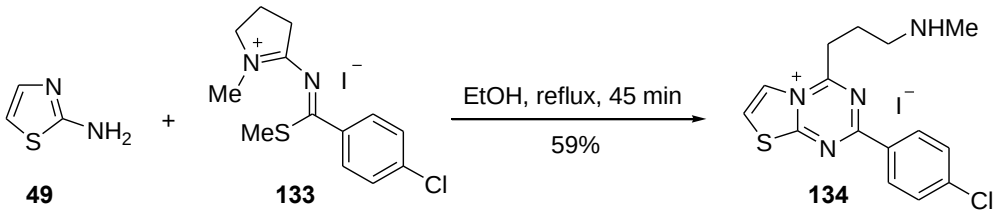
4-Dimethylamino-2-phenylthiazolo[3,2-*a*][1,3,5]triazinium perchlorate (**132**) was obtained by heating of 2-aminothiazole (**49**) with salt **131** in acetonitrile (Scheme 53).[67]



49 **131** **132**

Scheme 53

The reaction of 2-aminothiazole (**49**) with cyclic iminium salt **133** was reported[68] to afford thiazolo[3,2-*a*][1,3,5]triazinium iodide **134** (Scheme 54). When 4-substituted 2-aminothiazoles were used in the reaction, the triazine ring was not formed and only nucleophilic addition or substitution at the methyl thioimidate group of **133** and analogues occurred due to attack of the amino group of 2-aminothiazoles.

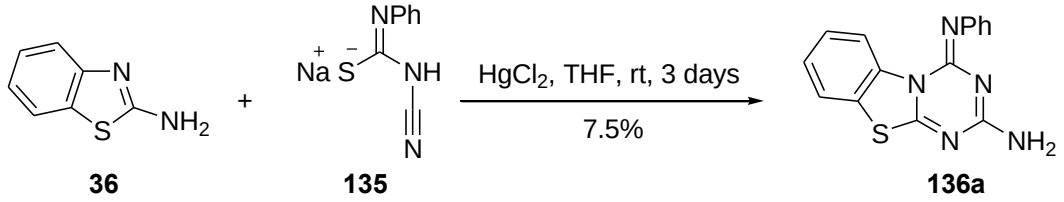


49 **133** **134**

Scheme 54

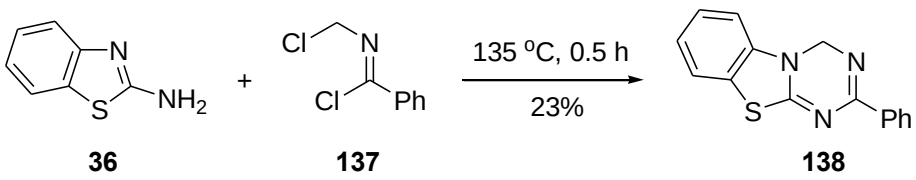
2-Amino-4-phenylimino-1,3,5-triazino[2,1-*b*]benzothiazole (**136a**) was prepared *via* reaction of 2-aminobenzothiazole (**36**) with sodium salt of *N*-cyano-*N'*-phenyl thiourea (**135**) (Scheme 55).[69] A

number of substituted analogues of **136**, claimed to possess immuno-regulant activity, were synthesized by this manner or using *N*-cyano-*N'*-phenyl-*S*-methyl isothiourea instead of **135**. However, low yields of the product, long reaction time and using toxic mercuric chloride were apparent limitations of the method.



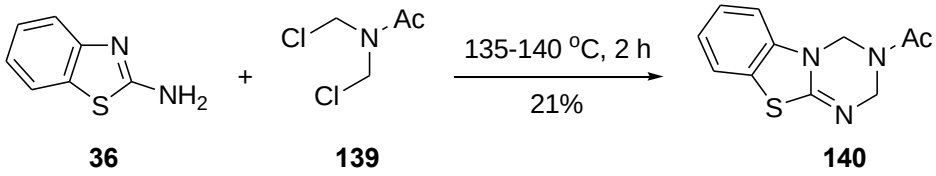
Scheme 55

Heating 2-aminobenzothiazole (**36**) with *N*-(chloromethyl)benzimidoyl chloride (**137**) was reported[70] to afford 2-phenyl-4*H*-1,3,5-triazino[2,1-*b*]benzothiazole (**138**) (Scheme 56). The assignment of structure **138** *vs.* its possible regioisomer was supported by the ^{13}C NMR spectral data.



Scheme 56

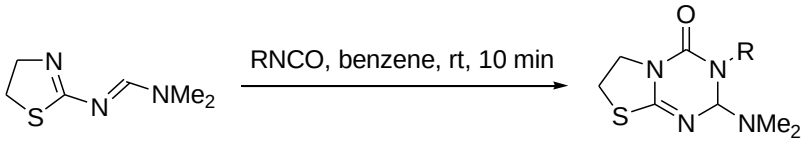
The reaction of 2-aminobenzothiazole (**36**) with *N*,*N*-bis(chloromethyl)acetamide (**139**) proceeded *via* double alkylation of endo- and exocyclic nitrogen atoms of **36**, thus resulting in the formation of 3-acetyl-3,4-dihydro-2*H*-1,3,5-triazino[2,1-*b*]benzothiazole (**140**) (Scheme 57).[71]



Scheme 57

2.1.5. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines *via* formal [4+2] cycloaddition.

Commonly, this strategy was realized in the reactions of hetero-1,3-dienes - aminothiazole derivatives as 4π-component with isocyanates and their analogues (2π-dienophiles). Thus, formamidine **21** upon treatment with aryl isocyanates in the mild conditions underwent [4+2] cycloaddition with the formation of **141** (Scheme 58).[16] The reaction was found to be exothermic and very sensitive to the conditions. Changing ratio of the reagents and temperature substantially affected the reaction pathway and composition of the products (*cf.* Scheme 9).

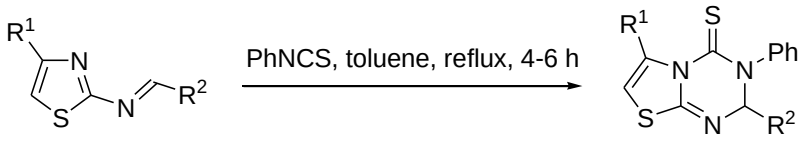


21 **141**

R = Ph, 91% (**141a**); 4-MeC_6H_4, 77% (**141b**)

Scheme 58

The cycloaddition of phenyl isothiocyanate to Schiff bases **58** was reported[72,73] to afford thiazolo[3,2-*a*][1,3,5]triazin-4-thiones **142** (Scheme 59).

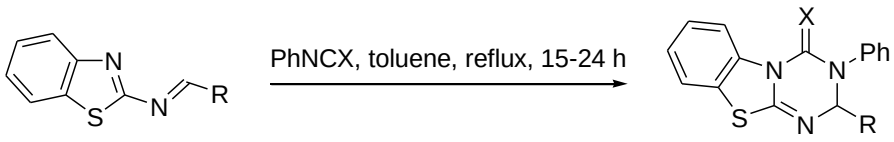


58 **142**

R^1 = 4-PhC_6H_4; R^2 = Ph, 57% (**142a**), 4-$(Me_2N)C_6H_4$, 49% (**142b**), 4-$NO_2C_6H_4$, 55% (**142c**)
R^1 = 5-(8-hydroxyquinolyl)-; R^2 = Ph, 65% (**142d**), 4-ClC_6H_4, 63% (**142e**), 4-$NO_2C_6H_4$, 62% (**142f**)

Scheme 59

Heating 2-(arylmethyleneamino)benzothiazoles (**29**) with phenyl isocyanate or phenyl isothiocyanate in toluene allowed the preparation of **143** (Scheme 60).[74] The reaction pathway was found[17] to strongly depend on the nature of the substituent R (*cf.* Scheme 12).

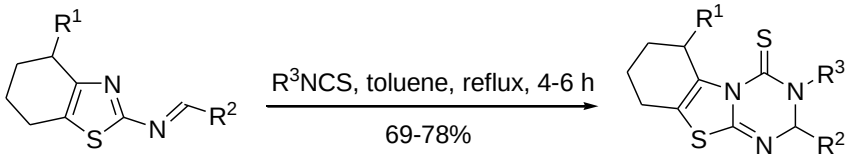


29 **143**

X = O; R = 4-ClC_6H_4, 60% (**143a**), 4-$NO_2C_6H_4$, 55% (**143b**)
X = S; R = 4-ClC_6H_4, 60% (**143c**), 4-$NO_2C_6H_4$, 50% (**143d**)

Scheme 60

Similarly, when Schiff bases **144** reacted with aryl isothiocyanates, tricyclic structures **145** were formed (Scheme 61).[75]

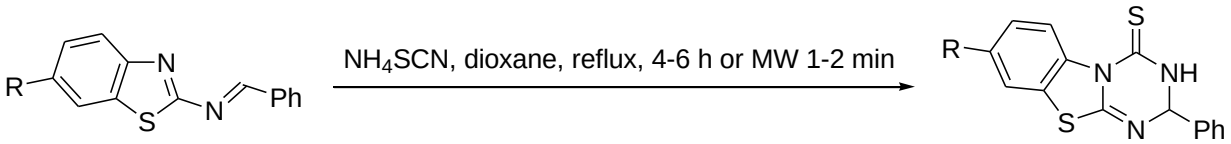


144 **145**

R^1 = H, Me; R^2 = 2-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4; R^3 = 4-ClC_6H_4, 4-MeC_6H_4

Scheme 61

The reaction of 2-(benzylidenamino)benzothiazoles (**146**) with ammonium thiocyanate resulted in the annulation of the triazine ring affording **147** (Scheme 62).[76,77] Using microwave irradiation was reported[77] to shorten the reaction time and improve yields. The antibacterial activity of **147** was evaluated.[77]

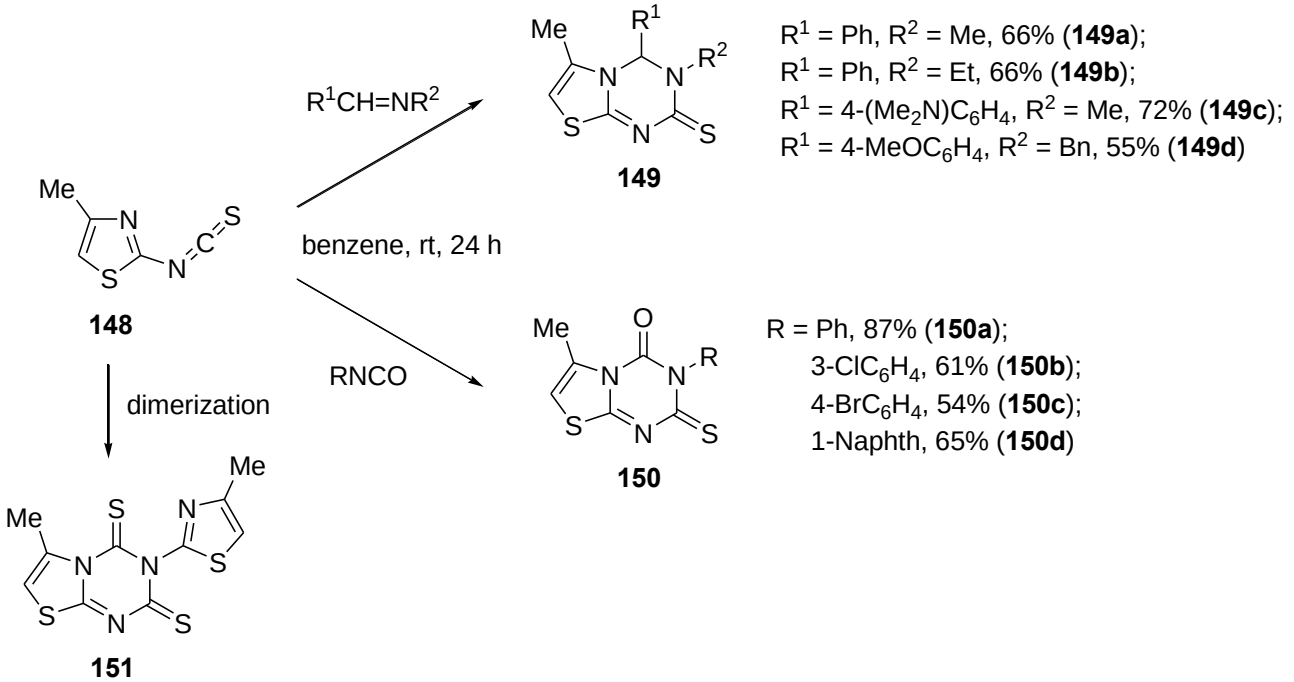


146 **147**

R = Cl, 70 or 88% (**147a**); Br, 55 or 70% (**147b**); NO_2, 49 or 66% (**147c**); OEt, 68 or 90% (**147d**)

Scheme 62

It was reported[78] that 2-(4-methyl)thiazolyl isothiocyanate (**148**) reacted with Schiff bases and aryl isocyanates providing thiazolo[3,2-*a*][1,3,5]triazin-2-thiones **149** and **150**, respectively (Scheme 63). Despite strong tendency to dimerization of **148**, dimer **151** (a side product in the synthesis of **148**) was not isolated from the reactions. Interestingly, no reaction was observed when 2-(4-phenyl)thiazolyl isothiocyanate was treated with aldimines or isocyanates even on heating.



148

149

R^1 = Ph, R^2 = Me, 66% (**149a**);
R^1 = Ph, R^2 = Et, 66% (**149b**);
R^1 = 4-$(Me_2N)C_6H_4$, R^2 = Me, 72% (**149c**);
R^1 = 4-$MeOC_6H_4$, R^2 = Bn, 55% (**149d**)

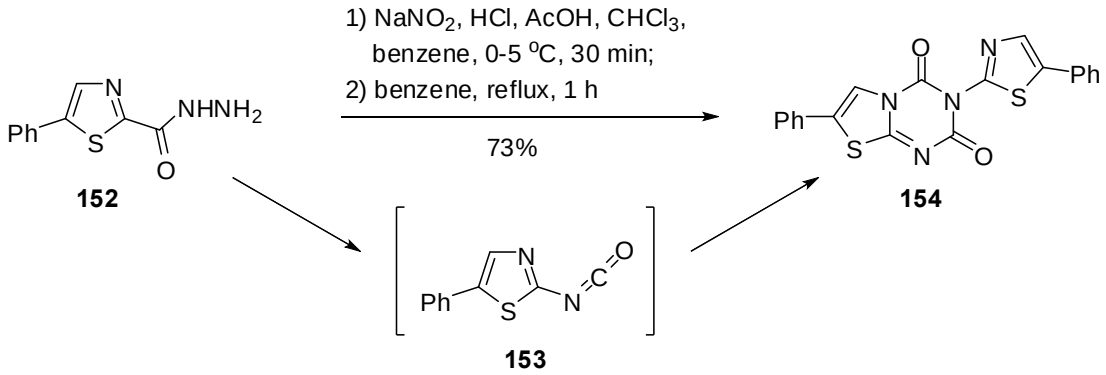
150

R = Ph, 87% (**150a**);
3-ClC_6H_4, 61% (**150b**);
4-BrC_6H_4, 54% (**150c**);
1-Naphth, 65% (**150d**)

151

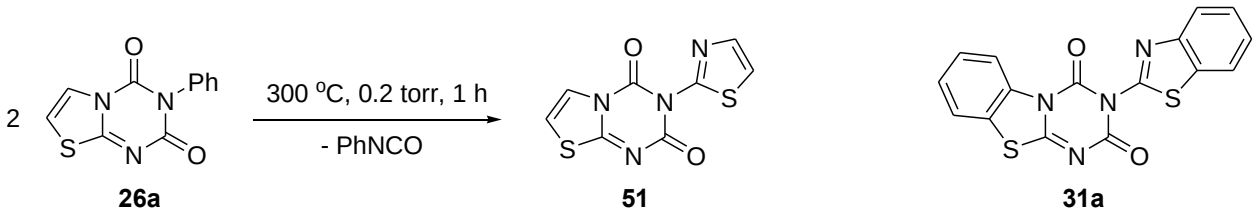
Scheme 63

The cyclodimerization of isocyanate **153**, derived from hydrazide **152**, resulted in the formation of thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione **154** (Scheme 64).[79]



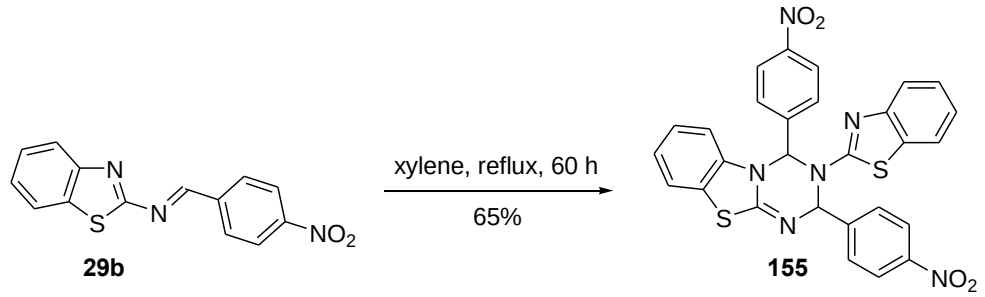
Scheme 64

It was found that 3-phenylthiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**26a**) on heating lost phenyl isocyanate and form **51** as a product of the cyclodimerization of 2-thiazolyl isocyanate (**50**) (Scheme 65).[23] Analogously, thermolysis of **28a** resulted in the formation of **31a** (*cf.* Schemes 12 and 21).



Scheme 65

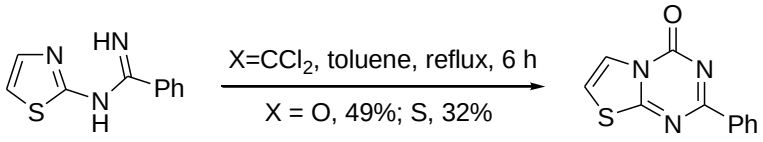
An example of the cyclodimerization of Schiff base **29b** was reported by Abdel-Rahman.[74] On prolonged heating in xylene, **29b** afforded cycloadduct **155** (Scheme 66).



Scheme 66

2.1.6. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines *via* 1,3,5-triazine ring annelation on 2-substituted thiazoles using one-carbon inserting reagents.

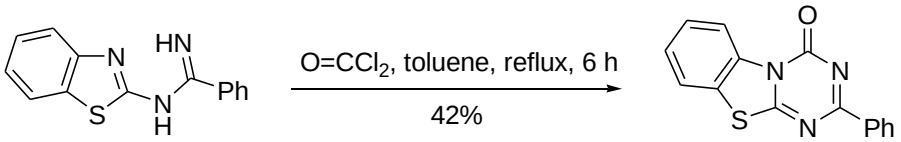
George and Tahilramani[80] reported synthesis of 2-phenylthiazolo[3,2-*a*][1,3,5]triazin-4-one (**157**) *via* inserting the carbonyl group by treatment of *N*-(thiazol-2-yl)benzamidine (**156**) with phosgene (Scheme 67). From the reaction of **156** with thiophosgene, **157** was isolated instead of the thiocarbonylation product (**82b**), which presumably underwent hydrolysis under the work-up conditions.



156 **157**

Scheme 67

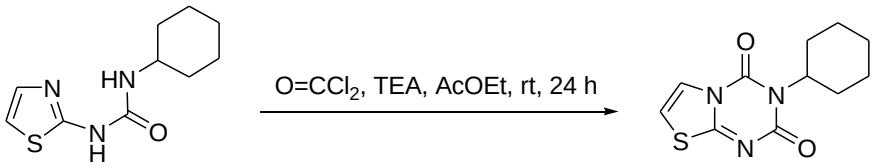
Similarly, benzofused analogue **130** was synthesized from *N*-(benzothiazol-2-yl)benzamidine (**158**) and phosgene (Scheme 68).[80]



158 **130**

Scheme 68

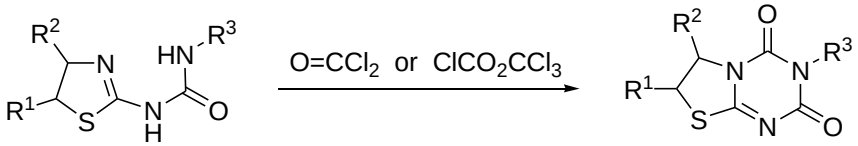
3-Cyclohexylthiazolo[3,2-*a*][1,3,5]triazine-2,4-dione (**160**) was prepared from urea **159** by treatment with phosgene in the presence of base (Scheme 69).[81] The product (**160**) was claimed to possess fungicidal properties.



159 **160**

Scheme 69

Similarly, thiazolidine substituted ureas **161** were converted to **162** by the treatment with phosgene or diphosgene (Scheme 70).[81-83] Compounds **162** were found to be useful as fungicides in agriculture.



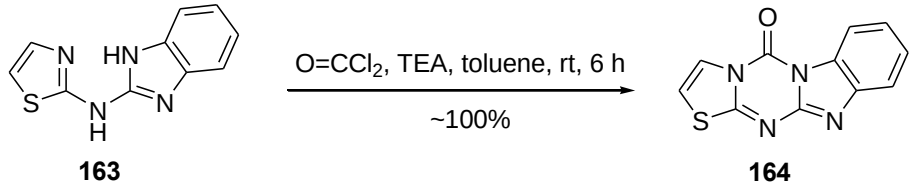
161 **162**

Scheme 70

Tetracyclic system **164** comprising thiazolo[3,2-*a*][1,3,5]triazin-4-one and benzimidazole was also prepared from 2-(thiazol-2-yl)benzimidazole (**163**) using phosgene as a one-carbon inserting reagent (Scheme 71).[84]

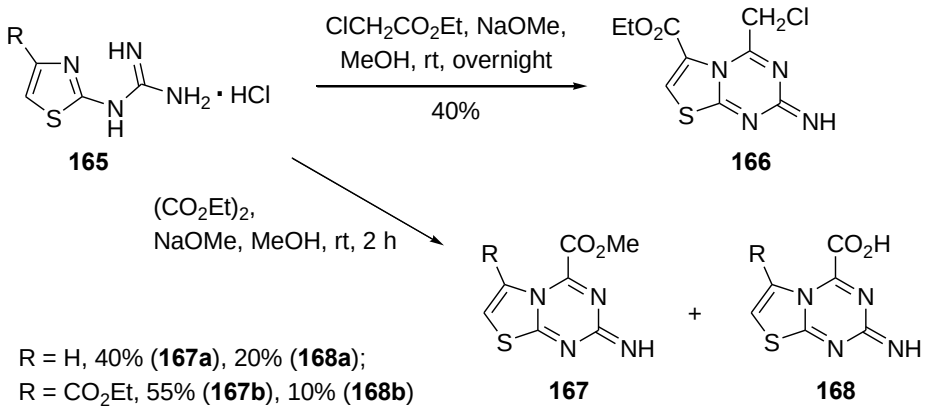
A variety of electrophilic reagents were adopted as one-carbon inserting reagents for the 1,3,5-triazine ring formation on the scaffold of thiazolyl and benzothiazolyl substituted guanidines. The reaction of 2-thiazolyl guanidines **165** with ethyl chloroacetate in the presence of sodium methylate was reported[85] to

afford thiazolo[3,2-*a*][1,3,5]triazine **166** (Scheme 72). In similar conditions, diethyl oxalate with **165** produced a mixture of methyl esters **167** and corresponding acids **168**.



163 **164**

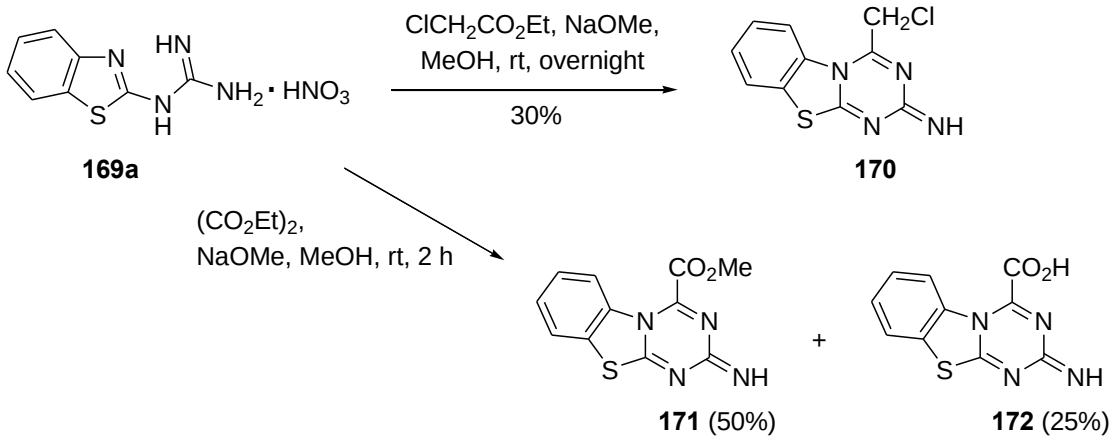
Scheme 71



165 **166** **167** **168**

Scheme 72

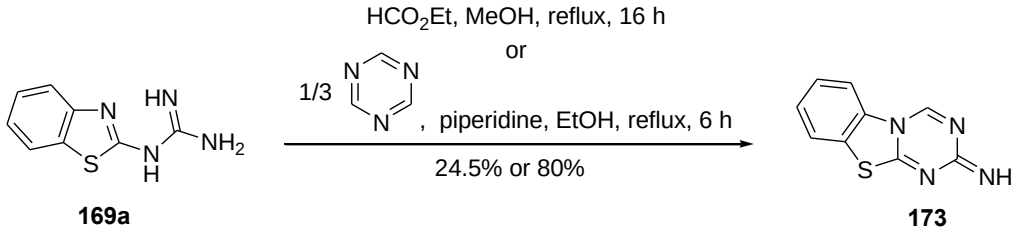
The analogous reaction of 2-benzothiazolylguanidine (**169a**) in with ethyl chloroacetate was applied for the synthesis of tricyclic **170** (Scheme 73).[85] The triazine ring closure of **169a** with diethyl oxalate resulted in the formation of mixture of **171** and **172**.



169a **170** **171** (50%) **172** (25%)

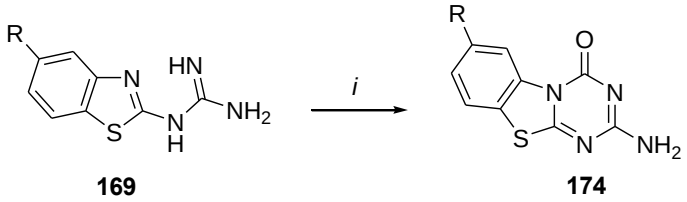
Scheme 73

Kreutzberger[86] reported the synthesis of 1,3,5-triazino[2,1-*b*]benzothiazol-2-imine (**173**) from 2-benzothiazolyl guanidine (**169a**) and ethyl formate (Scheme 74). The yield of **173** was improved by the replacement of ethyl formate with 1,3,5-triazine as one-carbon inserting reagent.



Scheme 74

The triazine ring closure with introduction of carbonyl group was achieved by treatment of 2-benzothiazolyl guanidines (**169**) with diethyl azodicarboxylate[87] or phenyl and tosyl isocyanates[88,89] (Scheme 75). The microwave irradiation was found to promote the reaction of **169** with phenyl isocyanate.[89]



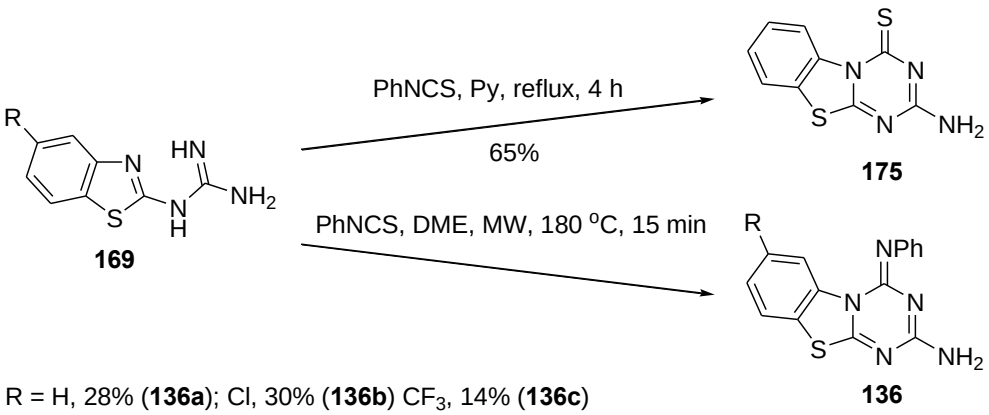
i: DEAD, dioxane, reflux, 12 h
R = H, 26% (**174a**);

i: TsNCO, dioxane, reflux, 4 h
R = H, 63% (**174a**);

i: PhNCO, DME, MW, 180 °C, 15 min
R = H, 96% (**174a**); Cl, 90% (**174b**); CF_3, 95% (**174c**

Scheme 75

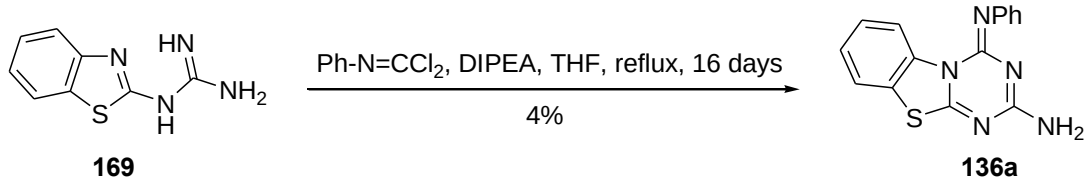
Depending on the conditions applied, two types of the heterocyclization products were isolated from the reaction of **169** with phenyl isothiocyanate (Scheme 76). Heating **169** with phenyl isothiocyanate in pyridine afforded ring closure thiocarbonylation product **175**.[88] Under microwave irradiation, 2-amino-4-phenylimino-1,3,5-triazino[2,1-*b*]benzothiazoles (**136**) were formed in the similar reaction.[89]



R = H, 28% (**136a**); Cl, 30% (**136b**) CF_3, 14% (**136c**)

Scheme 76

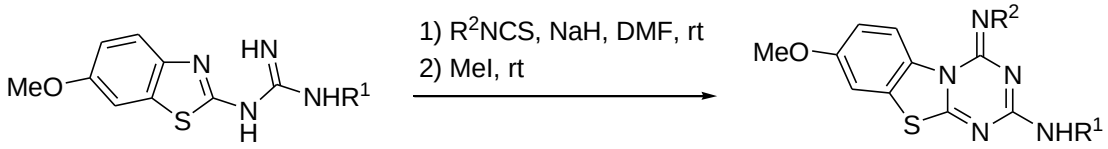
The synthesis of **136a** was also carried out *via* the cyclization of 2-benzothiazolyl guanidine (**169**) with phenyl isocyanide dichloride, but the yield was very low (Scheme 77).[69]



169 **136a**

Scheme 77

1,3,5-Triazino[2,1-*b*]benzothiazoles **177** were prepared form guanidines **176** by subsequent treatment with aryl isothiocyanate in the presence of sodium hydride followed by methyl iodide (Scheme 78).[69]



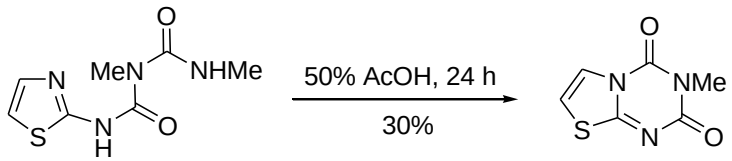
176 **177**

R^1 = H, Ph; R^2 = Ph, 4-($Et_2NCH_2CH_2O$)C_6H_4

Scheme 78

2.1.7. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines *via* intramolecular cyclization of 2-substituted thiazoles with the formation of 1,3,5-triazine ring.

Etienne and Bonte[90] found that in aqueous acetic acid, 2-thiazolyl substituted biuret **178** underwent intramolecular cyclization with methylamine elimination affording 3-methyl-thiazolo[3,2-*a*][1,3,5]triazin-2,4-dione (**179**) (Scheme 79).

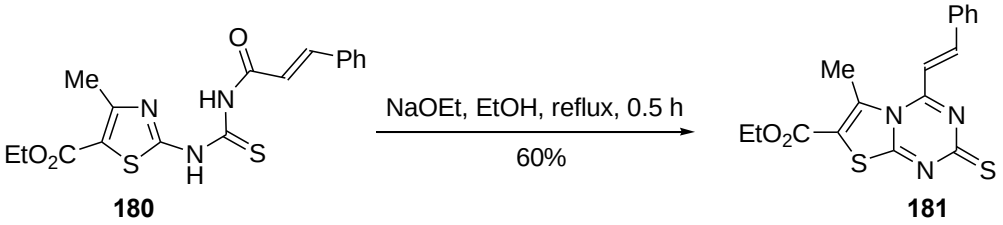


178 **179**

Scheme 79

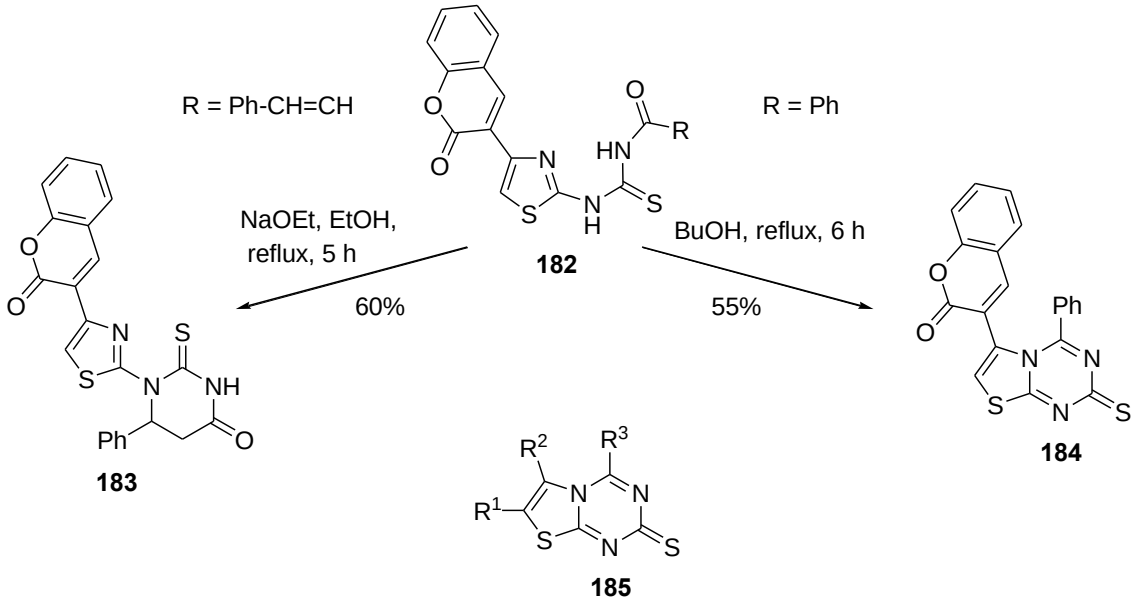
N-Acyl-*N'*-(2-thiazolyl)thioureas, prepared from 2-aminothiazoles and *N*-acyl isothiocyanates were used for the synthesis of a variety of substituted thiazolo[3,2-*a*][1,3,5]triazin-2-thiones. Thus, treatment *N*-cinnamoyl-*N'*-(2-thiazolyl)thiourea **180** with sodium ethoxide resulted in the 1,3,5-triazine ring annelation with the formation of **181** (Scheme 80).[91]

Interestingly, structurally related thiourea **182** (R = Ph-CH=CH) with 4-(3-coumaryl) substituent on the thiazole ring reacted differently in the similar conditions affording cycloaddition product **183** (Scheme 81).[92] However, heating *N*-benzoyl analogue **182** (R = Ph) in *n*-butanol was reported[92] to produce thiazolo[3,2-*a*][1,3,5]triazin-2-thione **184**.



Scheme 80

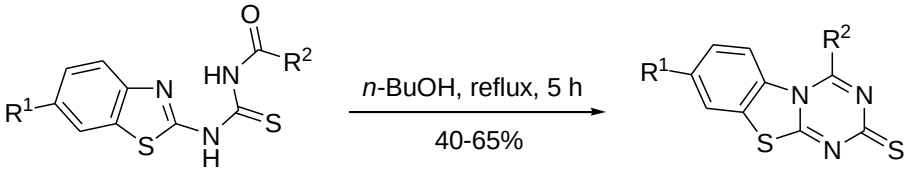
A number of thiazolo[3,2-*a*][1,3,5]triazin-2-thiones (**185**) were prepared *via* this type of cyclocondensation by heating of corresponding *N*-acyl-*N'*-(2-thiazolyl)thioureas with alkali,[93] phosphoryl chloride[94] or phosphoryl chloride/phosphorus pentachloride mixture.[95,96] The biological activity (antiviral,[95] antibacterial[94] and antifungal[96]) of **185** was also evaluated. However, lack of an appropriate structural characterization and controversy of the reported experimental data significantly decrease importance of the works.



Scheme 81

Heating *N*-aroyl-*N'*-(2-benzothiazolyl)thioureas **186** in butanol resulted in the 1,3,5-triazine ring closure with the formation of 4-aryl-1,3,5-triazino[2,1-*b*]benzothiazol-2-thiones **187** (Scheme 82).[97] The biological evaluation of **187** revealed anticonvulsant properties of the compounds in the maximum electroshock test in mice without signs of neurotoxicity or hepatotoxicity.

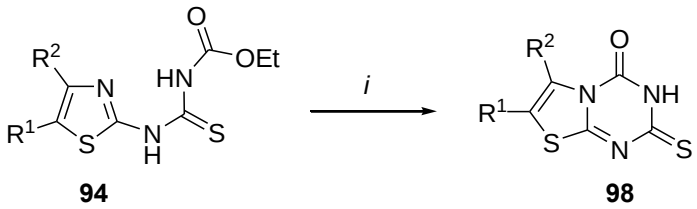
N-Ethoxycarbonyl-*N'*-(2-thiazolyl)thioureas (**94**), which were among products of the reaction of 2-aminothiazoles (**92**) with ethoxycarbonyl isothiocyanate (**84**) (*vide supra* Scheme 41), underwent thermal cyclocondensation affording 2-thioxothiazolo[3,2-*a*][1,3,5]triazin-4-ones **98** (Scheme 83).[57,58] The cyclization of *N*-ethoxycarbonyl-*N'*-(2-thiazolyl)thioureas (**94**) was also successfully induced by alkali.[98-100]



186 **187**

R^1 = H, F, Cl, Br, Me, OMe, NO_2
R^2 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 82

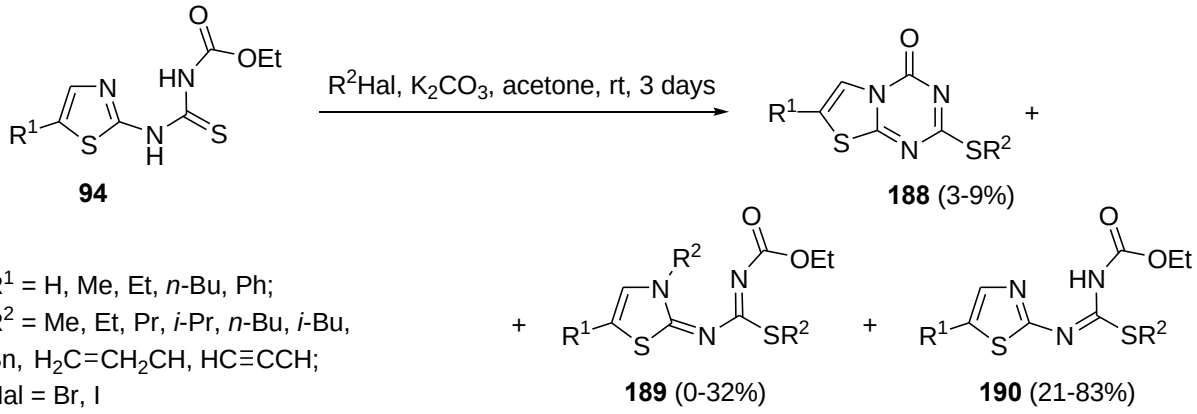


94 **98**

i: 180-190°C, 20 min
R^1 = R^2 = H, 25% (**98a**);
i: 5% NaOH, rt, 12 h
R^1 = H, R^2 = Ph, 58% (**98b**);
i: NaOEt, EtOH, reflux, 0.5 h
R^1 = CO_2Et, R^2 = Me, 90% (**98c**)

Scheme 83

From the reaction of *N*-ethoxycarbonyl-*N'*-(2-thiazolyl)thioureas (**94**) with alkyl halides in basic conditions, small quantities of thiazolo[3,2-*a*][1,3,5]triazin-4-ones **188** were isolated along with other alkylated products **189** and **190** (Scheme 84).[101]



94

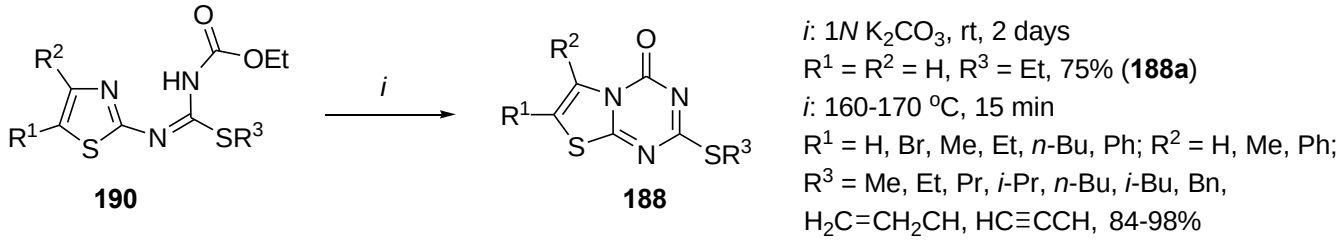
188 (3-9%)

189 (0-32%) **190** (21-83%)

R^1 = H, Me, Et, *n*-Bu, Ph;
R^2 = Me, Et, Pr, *i*-Pr, *n*-Bu, *i*-Bu, Bn, $H_2C{=}CH_2CH$, $HC{\equiv}CCH$;
Hal = Br, I

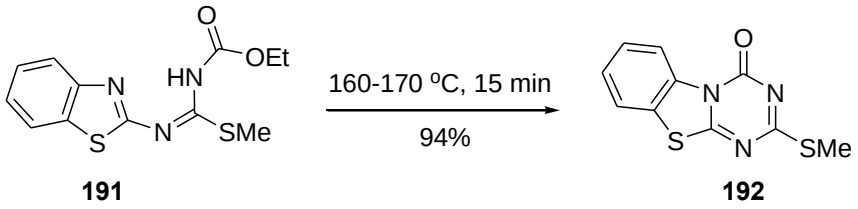
Scheme 84

In cases of alkylation of the thioureas substituted in position 4 of the thiazole ring as well as *N*-ethoxycarbonyl-*N'*-(5-bromothiazol-2-yl)thiourea, no formation of thiazolo[3,2-*a*][1,3,5]triazines was observed. In the presence of base or on heating, the major products of the reactions, isothioureas **190**, were able to undergo cyclocondensation affording **188** with good yields (Scheme 85).[101] Other alkoxycarbonyl analogues of **94** and corresponding **190** reacted in the same way.



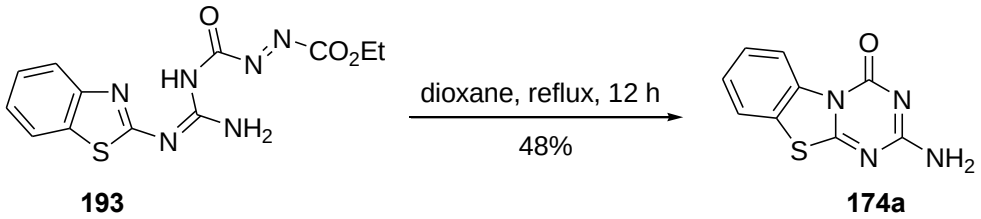
Scheme 85

The reaction of *N*-ethoxycarbonyl-*N'*-(2-benzothiazolyl)thiourea with methyl iodide in basic conditions did not result in the 1,3,5-triazine ring closure. However, the major product (79%) of the reaction, compound **191**, can be easily cyclized to 4-methylthio-1,3,5-triazino[2,1-*b*]benzothiazol-4-one (**192**) upon heating (Scheme 86).[101]



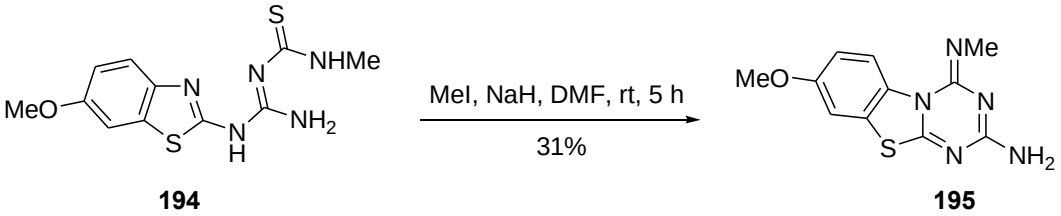
Scheme 86

The heterocyclization of **193**, which was isolated (46% yield) from the reaction of 2-benzothiazolyl guanidines (**169**) with diethyl azodicarboxylate in diethyl ether at room temperature, afforded **174a** (Scheme 87).[87] The synthesis of **174a** without isolation of intermediate **193** was also reported (*vide supra* Scheme 75).



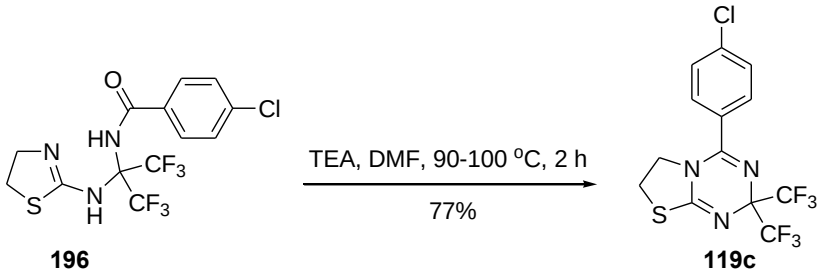
Scheme 87

The methylation of **194** was used to facilitate the 1,3,5-triazine ring closure providing **195** (Scheme 88).[69]



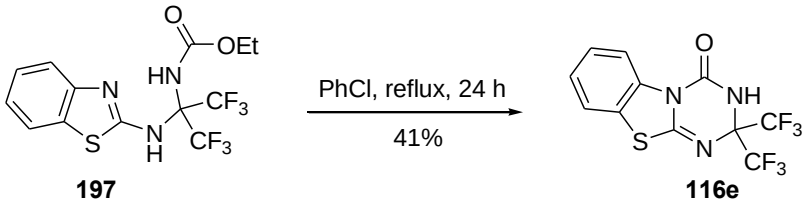
Scheme 88

The synthesis of 2,2-bis(trifluoromethyl)-4-(4-chlorophenyl)-6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazines (**119c**) was performed in the stepwise manner (*cf.* Scheme 49).[63] Adduct **196**, obtained with the 94% yield from the exothermic reaction between 2-aminothiazoline (**18**) and 4-chlorobenzoylimine of hexafluoroacetone (**118c**) in benzene, underwent further cyclization to give **119c** (Scheme 89).



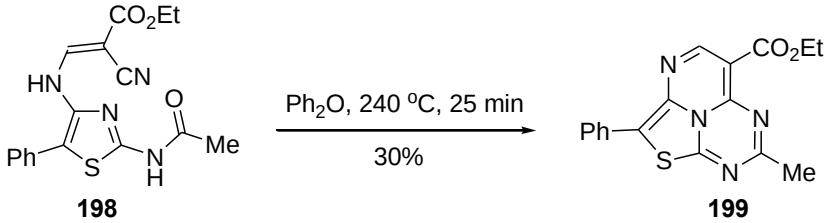
Scheme 89

The thermal cyclocondensation of **197**, prepared with the 91% yield by treatment of 2-aminobenzothiazole (**36**) with hexafluoroacetone ethoxycarbonylimine (**112**) in diethyl ether, afforded **116e** (Scheme 90).[102] The structure of the product (**116e**) was confirmed by X-ray crystallography. Sokolov and Aksinenko[62] used these data to support the regiochemistry of the direct synthesis of **116** from **36** and **112** without isolation of intermediates (*vide supra* Scheme 48).



Scheme 90

The pyrimidine and 1,3,5-triazine ring closure with formation of cyclazine **199** occurred when **198** was heated in diphenyl ether (Scheme 91).[103]

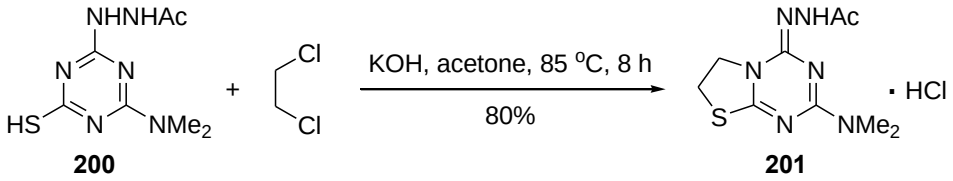


Scheme 91

2.2. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines by annelation of the thiazole ring onto a 1,3,5-triazine scaffold.

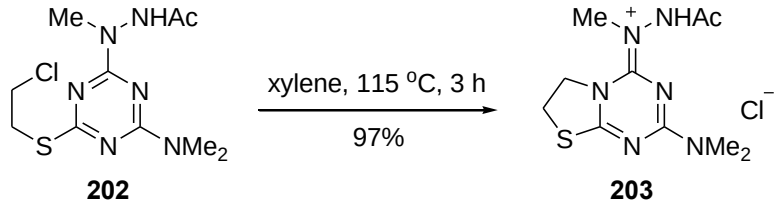
Even though the annelation of the thiazole ring onto a 1,3,5-triazine scaffold was the first method for the

synthesis of thiazolo[3,2-*a*][1,3,5]triazines (*vide supra* Scheme 1),[2,3] this approach has not been thoroughly explored. The main contributions to this field were done by Dovlatyan *et al.*,[104-108] who studied the reactions of 1,3,5-triazines with 1,2-dichloroethane and cyclizations of the 2-chloroethyl substituted 1,3,5-triazines. The reaction of triazine **200** with 1,2-dichloroethane in the presence of alkali was reported to result in the formation of salt **201**, which was converted to the corresponding free base (88% yield) by treatment with aqueous sodium hydroxide (Scheme 92).[104]



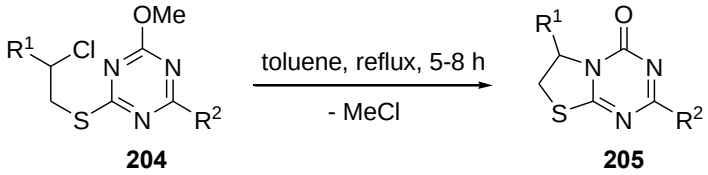
Scheme 92

The similar reaction of the methylated analogue of **200** provided triazine **202**, which underwent further cyclization to **203** upon heating in xylene (Scheme 93).[104]



Scheme 93

The cyclocondensation of 2-(2-chloroethylthio)-4-dialkylamino-6-methoxy-1,3,5-triazines (**204**) with elimination of methyl chloride was found to afford **205** (Scheme 94).[105,106] The detail mass-spectrometry investigation of the products **205** was also reported.[107]

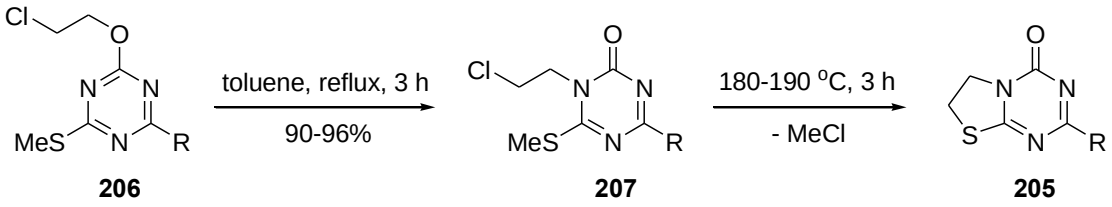


R^1 = H, R^2 = NMe_2, 90% (**205a**); NEt_2, 84% (**205b**);
R^1 = CN, R^2 = NMe_2, 94% (**205c**); NEt_2, 83% (**205d**)

Scheme 94

Compounds **205** were also prepared from triazines **206** *via* the translocative rearrangement to **207** and subsequent intramolecular cyclization with the methyl chloride elimination (Scheme 95).[108] The conversion of **206** into 2-dialkylamino-6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4-ones (**205**) was also performed by heating at 180-190 °C without isolation of **207**.

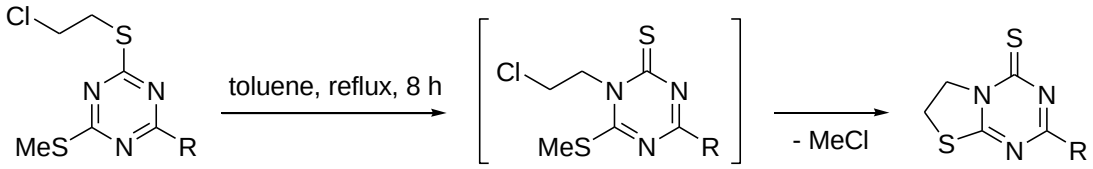
The similar synthesis of 2-dialkylamino-6,7-dihydrothiazolo[3,2-*a*][1,3,5]triazin-4-thiones (**210**) from corresponding **208** was proposed[105] to involve transfer of the chloroethyl group to the endocyclic nitrogen (Scheme 96). This pathway was suggested by intermediates **209**, which were isolated when the reaction was stopped after 15 min of heating **208** in toluene.



206 **207** **205**

R = NMe_2, 92% (**205a**); NEt_2, 96% (**205b**)

Scheme 95

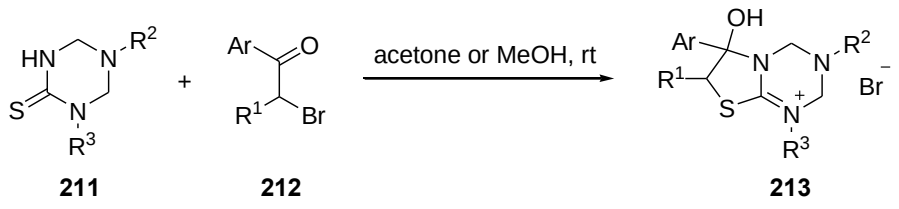


208 **209** **210**

R = NMe_2, 90% (**210a**); NEt_2, 85% (**210b**)

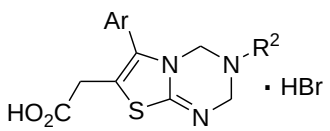
Scheme 96

The treatment of triazines **211** with bromoacetophenones (**212**, R^1 = H) in acetone resulted in the formation of salts **213** (Scheme 97), which were claimed[109] as potential antiulcer agents. The similar reaction of **211** with 3-aroyl-3-bromopropionic acids (**212**, R^1 = CH_2CO_2H) in methanol at ambient temperature afforded corresponding adducts **213**, which were able to increase survival time of the mice with P338 leukemia.[110] The dehydration products **214** were isolated when the reaction was carried out on heating.



211 **212** **213**

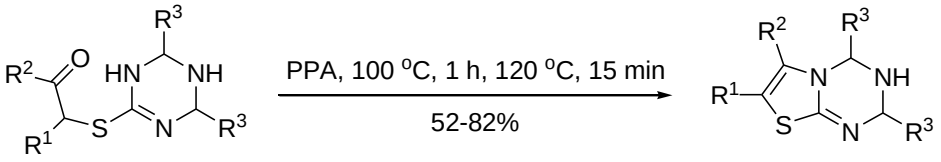
R^1 = H, CH_2CO_2H;
R^2 = Me, Et, CH_2=$CHCH_2$, Bn, 3-$MeOC_6H_4CH_2$;
R^3 = H, Me, CH_2=$CHCH_2$, Bn



214 R^2 = Bn, 3-$MeOC_6H_4CH_2$

Scheme 97

The cyclocondensation of **215** in polyphosphoric acid was reported[111] to produce **216** (Scheme 98). 2,4,6-Triphenyl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazine (**216a**, R^1 = H, R^2 = R^3 = Ph) was explored as a stabilizer for the single base propellant.[112]

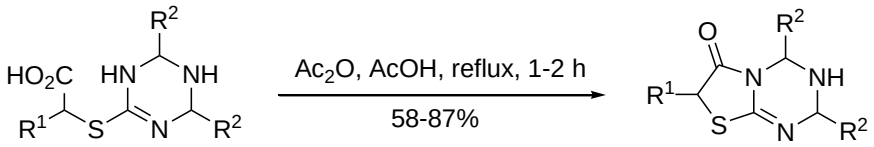


215 **216**

R^1 = H, Ac; R^2 = Me, Ph, 4-MeC_6H_4; R^3 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 98

Acids **217** were found to undergo intramolecular cyclization affording **218** (Scheme 99).[113,114] 2,4-Diphenyl-2,3,4,7-tetrahydrothiazolo[3,2-*a*][1,3,5]triazin-6-one (**218a**, R^1 = H, R^2 = Ph) was explored as a stabilizer for the double base propellant.[115]



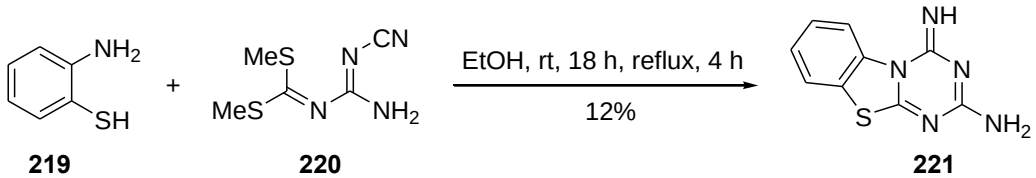
217 **218**

R^1 = H, Me; R^2 = Ph, 2-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$

Scheme 99

2.3. Synthesis of thiazolo[3,2-*a*][1,3,5]triazines *via* formation of the thiazole and 1,3,5-triazine ring.

2-Amino-4-imino-1,3,5-triazino[2,1-*b*]benzothiazole (**221**) was prepared from *o*-aminothiophenol (**219**) and substituted cyanoguanidine **220** *via* consecutive formation of the thiazole and triazine rings (Scheme 100).[69]



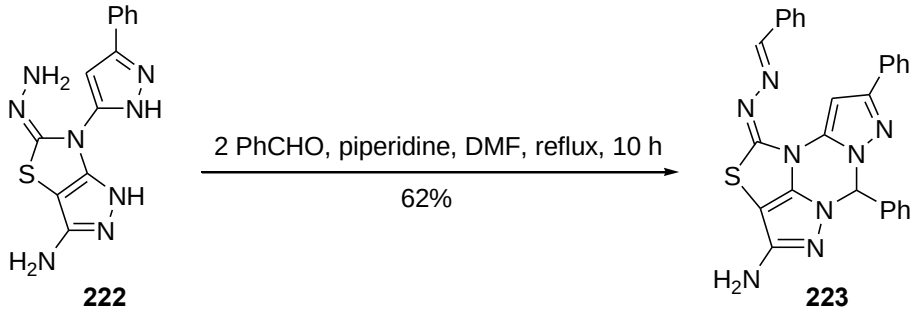
219 **220** **221**

Scheme 100

3. HETEROCYCLIC SYSTEMS COMPRISING THIAZOLO[3,4-*a*][1,3,5]TRIAZINE CORE

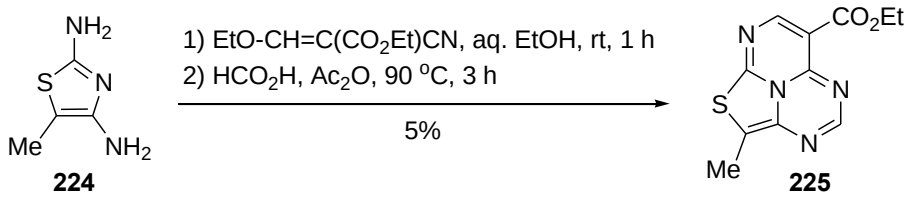
The 1,3,5-triazine ring fused with 3,4-side of thiazole has been reported only as a part of more complex heterocyclic systems. For example, tetracyclic compound **223** was formed by the condensation of **222** with benzaldelyde (Scheme 101).[116]

The cyclazines comprising the thiazolo[3,4-*a*][1,3,5]triazine and pyrimidine rings were synthesized by Ceder and Beijer.[103,117] The reaction of 2,4-diamino-5-methylthiazole (**224**) with ethyl 2-cyano-3-ethoxyacrylate followed by heating with acetic-formic anhydride resulted in the formation of 8-ethoxycarbonyl-4-methyl-5-thia-1,3,6-triazacycl[3.2.3]azine (**225**) with low yield (Scheme 102).[117]



222 **223**

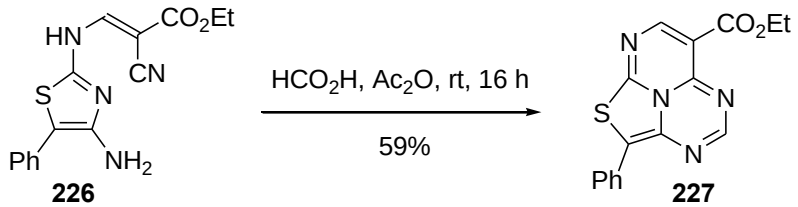
Scheme 101



224 **225**

Scheme 102

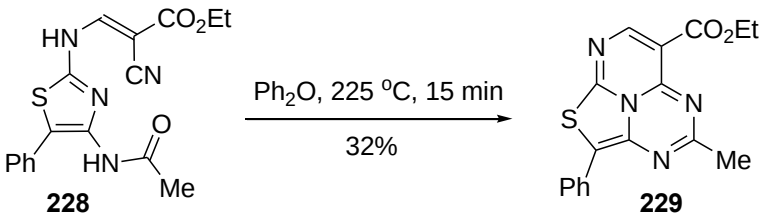
For the preparation of analogous phenyl substituted cyclazine **227**, intermediate **226** was isolated and converted to **227** by the treatment with acetic-formic anhydride at ambient temperature (Scheme 103).[103]



226 **227**

Scheme 103

The thermal cyclocondensation of **228**, a product of the acetylation of amine **226**, allowed the synthesis of **229** (Scheme 104).[103]



228 **229**

Scheme 104

4. CONCLUSION

A variety of effective methods for the preparation of thiazolo[3,2-*a*][1,3,5]triazines has been developed, mainly by the annelation of the 1,3,5-triazine ring onto a 1,2,4-triazole scaffold. The spectrum of known biological activities of compounds bearing thiazolo[3,2-*a*][1,3,5]triazine skeleton includes antitumor, antiviral, antibacterial, antifungal, anthelmintic, and anticonvulsant activities. The examples of the phospholipase C-γ inhibitors, 5-HT_2-receptor antagonists, and selective DNA binding agents have been reported. However, these data are sporadic and more systematic medicinal chemistry investigations of thiazolo[3,2-*a*][1,3,5]triazines are required. The present review aims to serve as a background for the research in this area.

The chemistry of thiazolo[3,4-*a*][1,3,5]triazines remains in the initial development stages and its potential is to be discovered in future.

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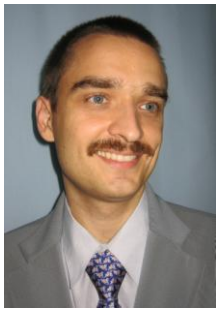

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