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SYNTHETIC ROUTES TOWARDS PYRIMIDO[1,2-*a*][1,3,5]TRIAZINES (REVIEW)[1]

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Abstract – The present review summarizes information on the synthetic approaches to compounds with pyrimido[1,2-*a*][1,3,5]triazines, 1,3,5-triazino[2,1-*b*]quinazolines (benzofused pyrimido[1,2-*a*][1,3,5]triazines), and other polyfused heterocyclic systems bearing these scaffolds. Data concerning potential applications of the pyrimido[1,2-*a*][1,3,5]triazines, particularly as biologically active agents, are also discussed.

CONTENTS

1. INTRODUCTION

In continuation of the series of reviews on fused 1,3,5-triazines,[1] the present review focuses on existing methods of the synthesis of compounds comprising pyrimido[1,2-*a*][1,3,5]triazine nucleus (Figure 1) as well as their biological activity and applications.

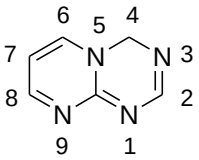
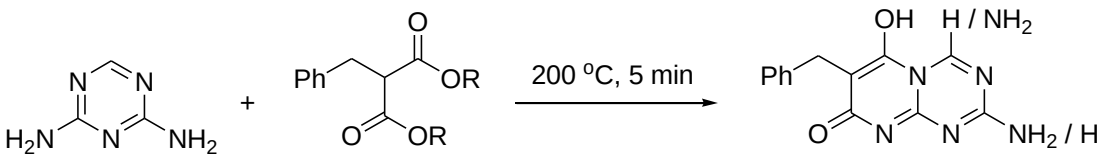


Figure 1

The first publication on the synthesis of pyrimido[1,2-*a*][1,3,5]triazine derivative appeared 50 years ago.[2] Ziegler and Nölken[2] reported the reaction of 2,4-diamino-1,3-5-triazine (**1**) with *bis*-(2,4-dichlorophenol) ester of 3-benzylmalonic acid (**2**) that afforded pyrimido[1,2-*a*][1,3,5]triazine **3** (Scheme 1). However, they were not able to differentiate between two possible regioisomeric structures with amino group in position 2 or 4.



1 **2** **3**

R = 2,4-$Cl_2C_6H_3$

Scheme 1

Until now, a number of effective synthetic procedures has been developed for the preparation of diversely substituted pyrimido[1,2-*a*][1,3,5]triazines and their polyfused analogues. During last decade, an interest has been developed towards the biological activity investigation of compounds with the pyrimido[1,2-*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.

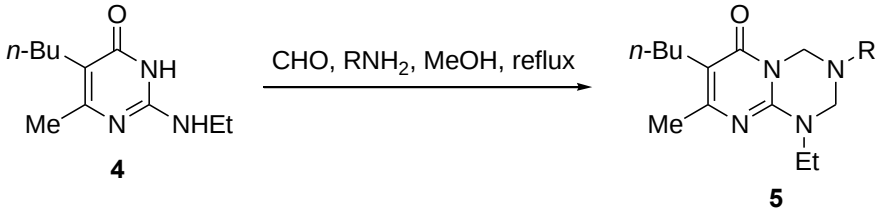
The general methods of synthesis of pyrimido[1,2-*a*][1,3,5]triazines can be categorized into: (1) annelation of the 1,3,5-triazine ring onto a pyrimidine scaffold, (2) annelation of the pyrimidine ring onto a 1,3,5-triazine scaffold, (3) formation of both pyrimidine and 1,3,5-triazine rings in the same reaction, and (4) rearrangements in pyrimido[1,2-*a*][1,3,5]triazines with recyclization of the system.

2. SYNTHESIS OF PYRIMIDO[1,2-*a*][1,3,5]TRIAZINES BY ANNELATION OF THE 1,3,5-TRIAZINE RING ONTO A PYRIMIDINE SCAFFOLD

The annelation of the 1,3,5-triazine ring onto a pyrimidine scaffold is the most explored and developed approach for the synthesis of pyrimido[1,2-*a*][1,3,5]triazines and their polyfused analogues. This section of the review is further subdivided on the basis of the reaction type and structure of the building blocks used in this approach.

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

The synthesis of pyrimido[1,2-*a*][1,3,5]triazines **5** was achieved *via* Mannich condensation of 2-ethylaminopyrimidine **4** with formaldehyde and variety of amines (Scheme 2).[3] The products were claimed as fungicides against plant-pathogenic fungi.



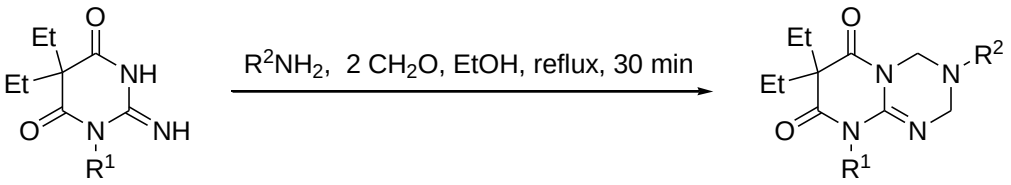
4 **5**

R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *c*-Hexyl, *n*-C_8H_{17}, *n*-$C_{18}H_{37}$, allyl, Bn, HO_2CCH_2, Ph

Scheme 2

The reaction of 5,5-diethyl substituted 2-imino analogues of barbituric acid **6** with formaldehyde and aliphatic amines was reported to result in the 1,3,5-triazine ring formation providing **7** (Scheme 3).[4,5] Similar reaction was performed using condensation of formaldehyde with **6** and a variety of anilines (Scheme 4). The yields of pyrimido[1,2-*a*][1,3,5]triazines **8** varied from 6 to 77% depending on the structure of the anilines used for the reaction.[6] The pharmacological screening of **8** led to the

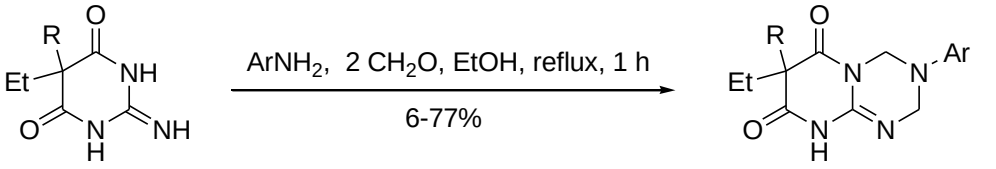
identification of one compound (R = Et, Ar = 2-ClC_6H_4) with antifungal activity against *Microsporum canis* ($10^{-6} < IC_{50} < 10^{-5}$ M) and another one (R = *n*-Bu, Ar = 4-$CF_3C_6H_4$) with average affinity for 5-HT_{1A} and 5-HT_{2B} receptors ($10^{-8} < IC_{50} < 10^{-7}$ M).



6 **7**

R^1 = H, R^2 = *i*-Pr (**7a**); Bn, 91% (**7b**);
R^1 = Me, R^2 = Bn, 65% (**7c**)

Scheme 3

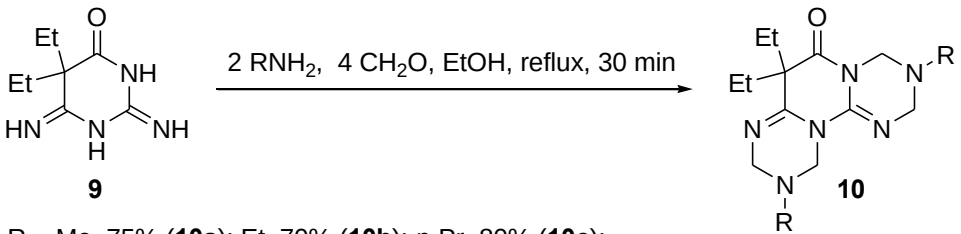


6 **8**

R = Me, Et, *n*-Pr, *n*-Bu;
Ar = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,3-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 2-$CF_3C_6H_4$, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 3-CF_3-4-ClC_6H_3

Scheme 4

The formation of two 1,3,5-triazine rings were observed when pyrimidine **9** possessing two imino groups underwent Mannich condensation with formaldehyde and amines (Scheme 5).[4,5] Tricyclic products **10** underwent biological investigation; **10d** and **10e** showed some anthelmintic activity against *Nippostrongylus brasiliensis*.[5]



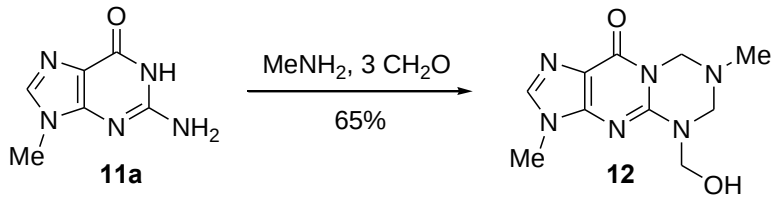
9 **10**

R = Me, 75% (**10a**); Et, 70% (**10b**); *n*-Pr, 80% (**10c**);
i-Pr, 75% (**10d**); Bn, 83% (**10e**); Ph, 60% (**10f**)

Scheme 5

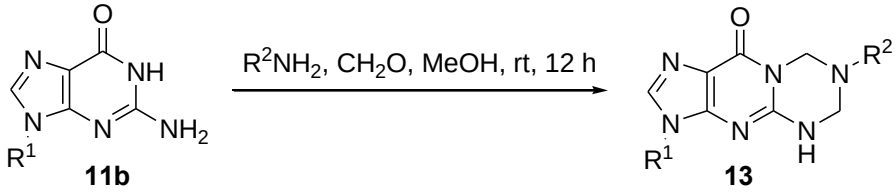
The reactions of nucleic bases with formaldehyde in presence of amines have been a subject of extensive explorations. Mannich condensation of different guanine derivatives were studied in various conditions.

Treatment of 9-methylguanine (**11a**) with formaldehyde and methylamine provided **12** as a product of the 1,3,5-triazine ring annelation and hydroxymetylation (Scheme 6).[7]



Scheme 6

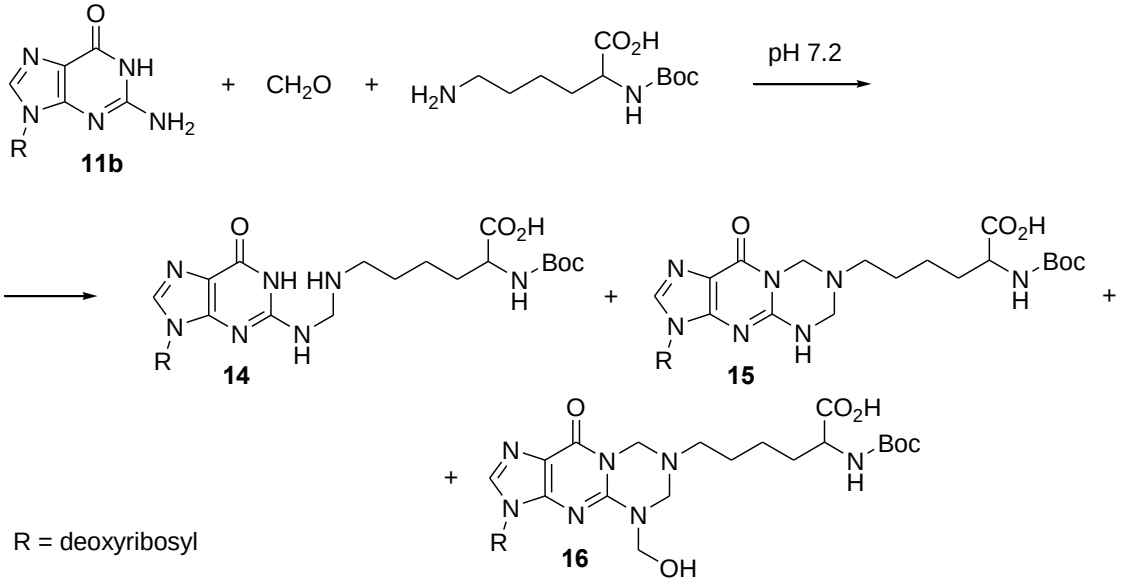
Takahashi and Hashimoto[8] reported synthesis of Mannich bases **13** using deoxyguanosine (**11b**), formaldehyde and butylamine or aniline (Scheme 7). This reaction was suggested as a possible model of the modification of DNA with carcinogenic amines in the formaldehyde presence.



R^1 = deoxyribosyl, R^2 = *n*-Bu, 80% (**13a**); Ph, 76% (**13b**)

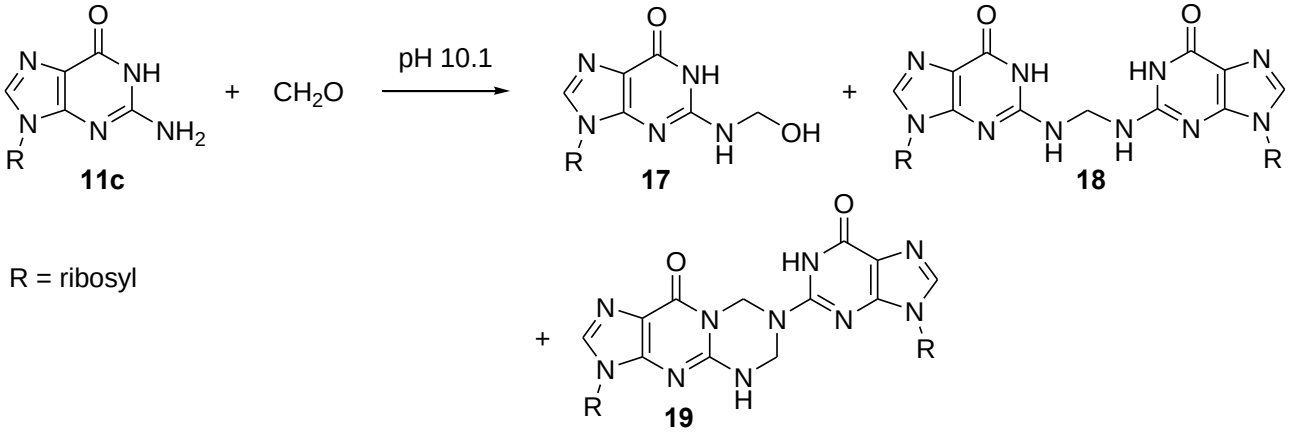
Scheme 7

To get a better understanding of carcinogenic and mutagenic properties of formaldehyde itself, the formaldehyde-induced cross-linking of deoxynucleosides with amino acids was investigated.[9] Mannich bases **15** and **16** were isolated together with another cross-linked product **14** from the reaction of deoxyguanosine (**11b**), formaldehyde and protected lysine (Scheme 8). The similar behavior was also observed for peptides containing lysine and trinucleotides containing deoxyguanosine (**11b**).



Scheme 8

The treatment of guanosine (**11c**) with formaldehyde in alkaline conditions resulted in the formation of N^2-hydroxymethylguanosine (**17**), bis-(N^2-guanosyl)methane (**18**), and tricyclic product **19** (Scheme 9).[10] For the structure assignments, ^{13}C- and ^{15}N-labelled **19** were also prepared using [^{13}C]formaldehyde and [^{15}N]guanosine. This reaction pathway was proposed to contribute to the genotoxic properties of formaldehyde.

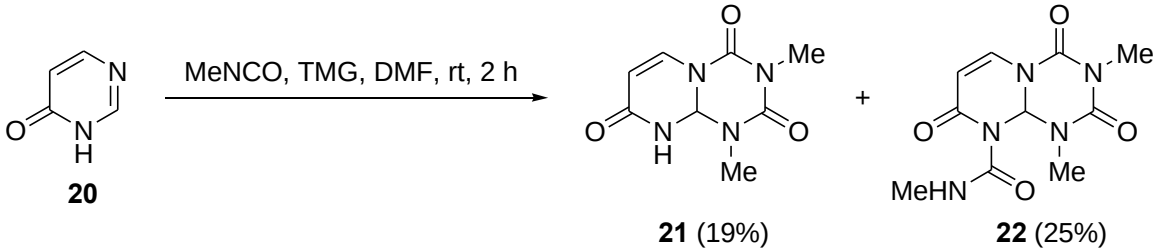


Scheme 9

2.2. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines using multicomponent reactions of pyrimidine derivatives with heterocumulenes

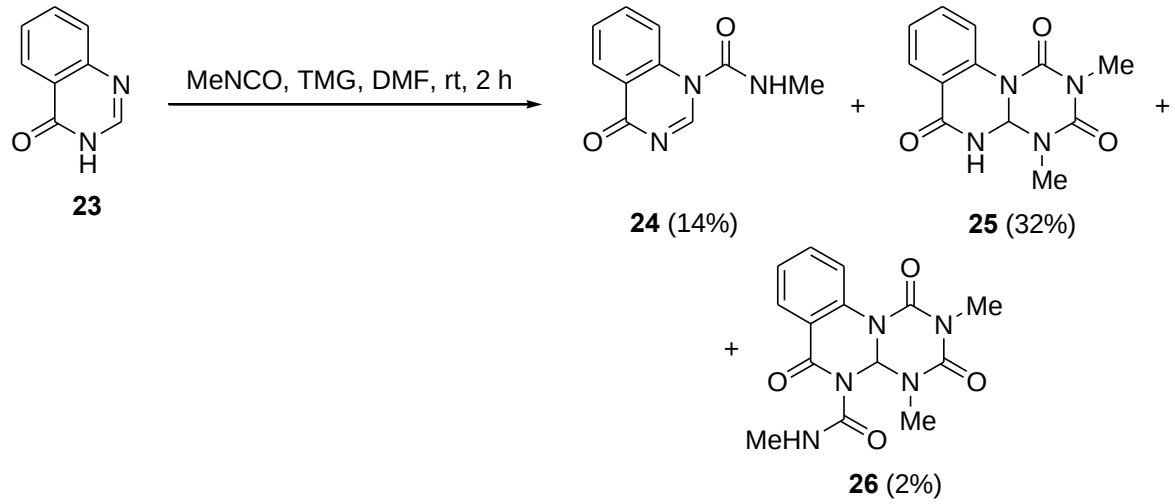
Several types of reactions with different mechanisms involved in the 1,3,5-triazine ring annelation process were reported for pyrimidine derivatives and isocyanates (most commonly used heterocumulenes). The key element of these reactions is cycloaddition, which may be accompanied by other processes depending on the substrate structure and the reaction conditions. The most explored approaches include: [2+2+2] cycloaddition of two iso(thio)cyanate molecules to substituted pyrimidine, reactions of pyrimidines having a leaving group in position 2, and reactions of 2-aminopyrimidines or their derivatives with heterocumulenes.

4-Pyrimidinone (**20**) in the reaction with methyl isocyanate in presence of base afforded mixture of 1:2-cycloadduct **21** and its methylcarbamoyl derivative **22** (Scheme 10).[11] Substantial amount (45%) of unreacted **20** was also recovered.



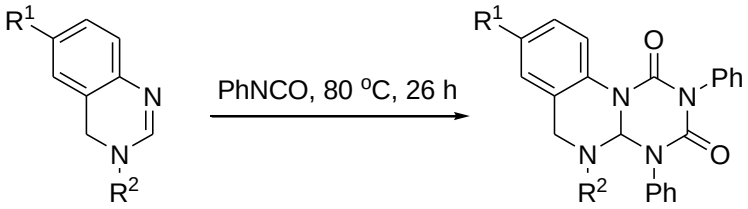
Scheme 10

Similarly, cycloadduct **25** was the main product of the reaction of 4-quinazolinone (**23**) with methyl isocyanate (Scheme 11).[11] Adducts **24** and **26** with 52% of unreacted **23** were also isolated from the reaction mixture.



Scheme 11

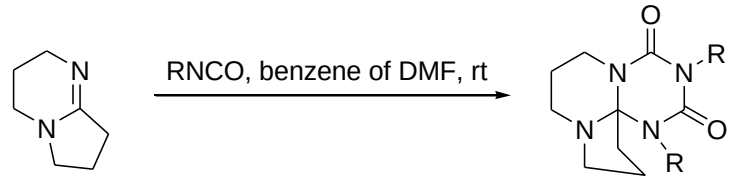
Under mild conditions, treatment of 3,4-dihydroquinazolines **27** with phenyl isocyanate led to the [2+2+2] cycloaddition providing **28** (Scheme 12).[12] The structure of the product was supported by X-ray crystallographic data for **28b**. Using higher temperatures in this reaction resulted in the formation of more complex cycloadducts.



R^1 = H, R^2 = Me, 83% (**28a**); R^2 = Bn, 48% (**28b**);
R^1 = Me, R^2 = 4-MeC_6H_4, 49% (**28c**)

Scheme 12

Richter[13] found that reaction of cyclic amidine **29** with phenyl and 4-chlorophenyl isocyanates in benzene under mild conditions afforded **30f** and **30i**, respectively (Scheme 13). Later, Arya and Shenoy[14] extended scope of this reaction for the synthesis of **30** applying isocyanates of diverse structure. Using DMF as a reaction media was also reported[15] for the preparation of **30a**.

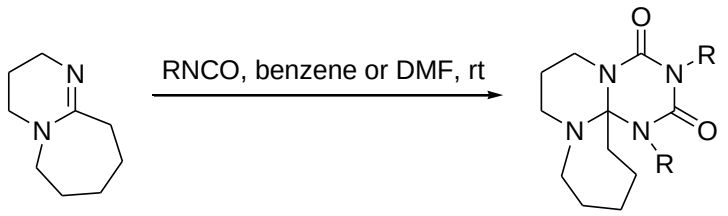


29 **30**

R = Me, 51% (**30a**); $ClCH_2CH_2$, 90% (**30b**); Bn, 87% (**30c**);
$PhCH_2CH_2$, 66% (**30d**); 2-Ph-cyclopropyl, 50% (**30e**);
Ph, 78% (**30f**); 2-$MeOC_6H_4$, 66% (**30g**); 4-FC_6H_4, 75% (**30h**);
4-ClC_6H_4, 86% (**30i**); 3,4,5-$(MeO)_3C_6H_2$, 60% (**30j**)

Scheme 13

Analogous synthesis of **32** was performed by treatment of amidine **31** with isocyanates in DMF (for **32a-c**)[15] or benzene (for **32d-j**)[14] (Scheme 14). These reactions were used in the invention[16] of heat-resistant coating and molding materials.

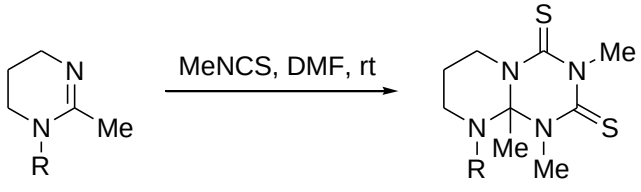


31 **32**

R = Me, 63% (**32a**); $MeOCH_2$, 74% (**32b**); $C_{14}H_{29}$, 90% (**32c**);
$ClCH_2CH_2$, 38% (**32d**); CH_2=$CHCH_2$, 70% (**32e**);
EtO_2CCH_2, 30% (**32f**); Bn, 40% (**32g**); $PhCH_2CH_2$, 37% (**32h**);
4-$MeOC_6H_4CH_2CH_2$, 10% (**32i**); Ts, 50% (**32j**)

Scheme 14

The cycloaddition of two molecules of methyl isothiocyanate to 2-methyl-1,4,5,6-tetrahydropyrimidines (**33**) resulted in the formation of pyrimido[1,2-*a*][1,3,5]triazines **34** (Scheme 15).[17] The reaction time was increased from 1-3 h for the synthesis of **34a,b** to 2 days for the preparation of phenyl substituted **34c**. The later was also obtained in 38% yield using chloroform as a solvent.

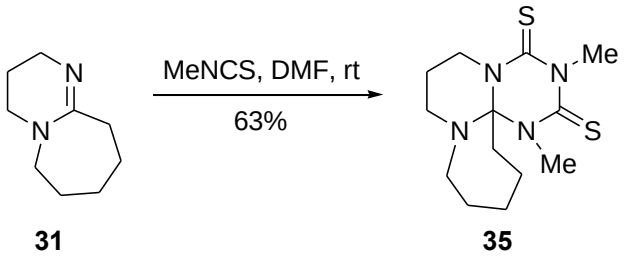


33 **34**

R = H, 87% (**34a**);
Me, 59% (**34b**);
Ph, 77% (**34c**)

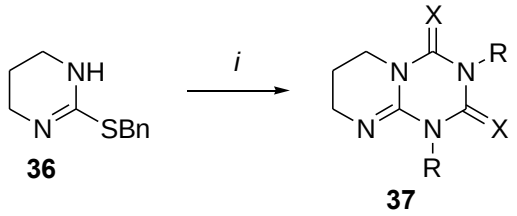
Scheme 15

Similar reaction of cyclic amidine **31** with methyl isothiocyanate afforded **35** (Scheme 16).[15]



Scheme 16

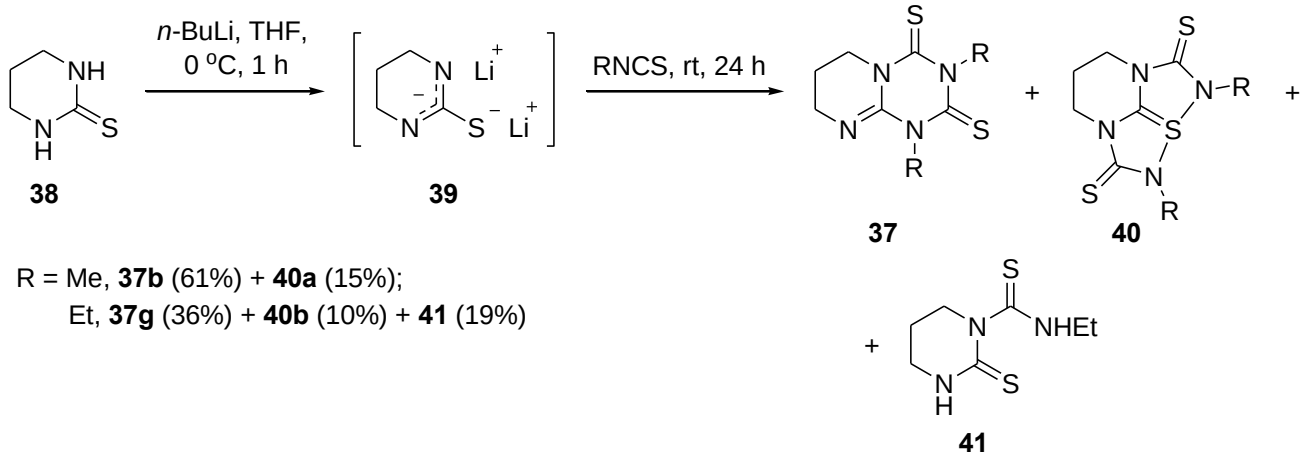
The reaction of 2-benzylthio-1,4,5,6-tetrahydropyrimidine (**36**) with phenyl isocyanate at ambient temperature led to the formation of pyrimido[1,2-*a*][1,3,5]triazin-2,4-dione **37a** (Scheme 17).[18] The benzylthio group served as a leaving group in this reaction. Similarly, a variety of isothiocyanates was successfully applied for the preparation of **37b-f**.[18-20] Using excess of isothiocyanates significantly improved yields of the products. However, attempts to prepare **37f** in benzene failed and despite excess of the isothiocyanate, only 5% of the product was isolated from the reaction in DMF.[20]



37	X	R	*i*	Yield, %
a	O	Ph	PhNCO (2 eq.), benzene, rt	53
b	S	Me	MeNCS (2 eq.), rt	54
c	S	Bn	BnNCS (2 eq.), benzene, rt	94
d	S	Ph	PhNCS (1 eq.), benzene, rt	15
			PhNCS (2 eq.), benzene, rt	30
			PhNCS (3 eq.), rt, 4 days	70
e	S	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$NCS (1 eq.), benzene, rt	25
			4-$NO_2C_6H_4$NCS (2 eq.), benzene, rt	59
f	S	4-$Me_2NC_6H_4$	4-(Me_2N)C_6H_4NCS (3.5 eq.), DMF, rt	5

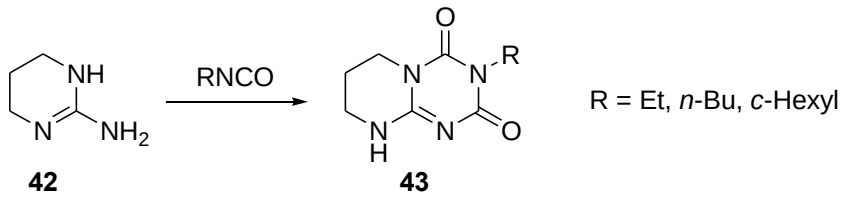
Scheme 17

Dianion **39**, generated from hexahydropyrimidin-2-thione (**38**), reacted with alkyl isothiocyanates also providing pyrimido[1,2-*a*][1,3,5]triazines **37** as main products. Moreover, tricyclic compounds **40** with hypervalent sulfur in the structure were formed at the same time (Scheme 18).[21] In case of the reaction of **39** with ethyl isothiocyanate, 1:1 adduct **41** was also isolated.



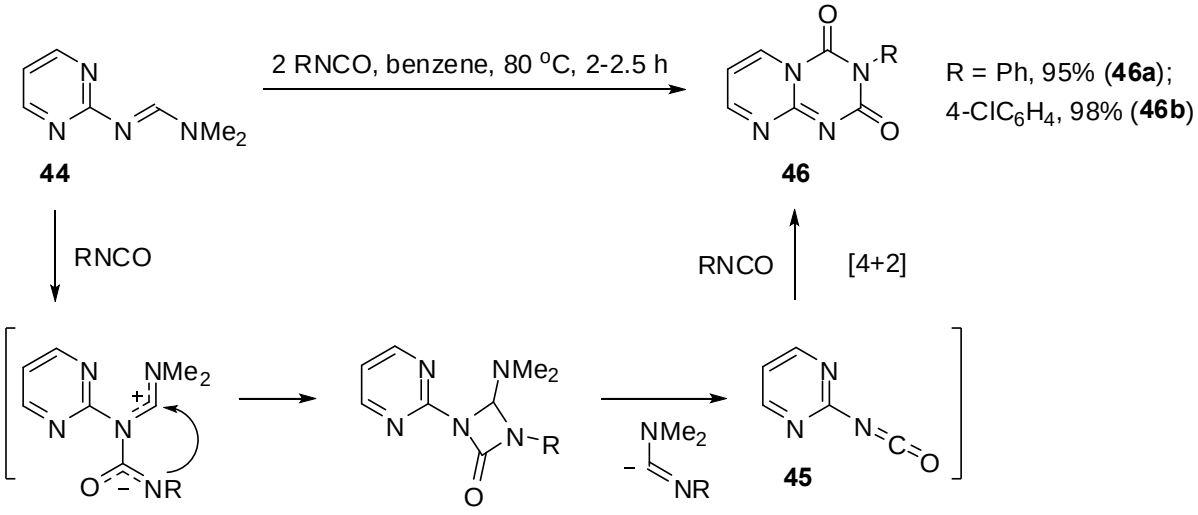
Scheme 18

The treatment of 2-amino-1,4,5,6-tetrahydropyrimidine (**42**) with isocyanates was claimed[22] to afford pyrimido[1,2-*a*][1,3,5]triazin-2,4-diones **43** possessing herbicidal properties (Scheme 19).



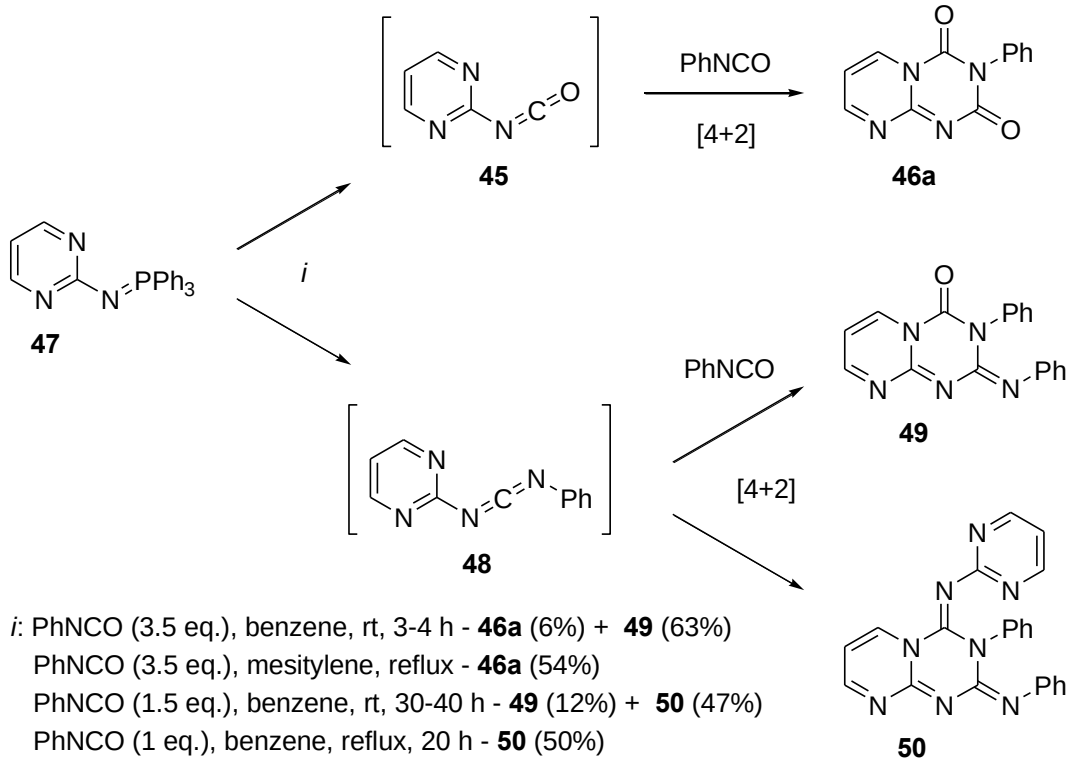
Scheme 19

Heating *N*,*N*-dimethyl-*N'*-(pyrimidin-2-yl)formamidine (**44**) with excess of aryl isocyanates in benzene gave 3-arylpyrimido[1,2-*a*][1,3,5]triazin-2,4-diones (**46**) (Scheme 20).[23] As a possible mechanistic explanation of the formation of **46**, [4+2] cycloaddition of presumable intermediate pyrimidin-2-yl isocyanate (**45**) and aryl isocyanate molecule was suggested.



Scheme 20

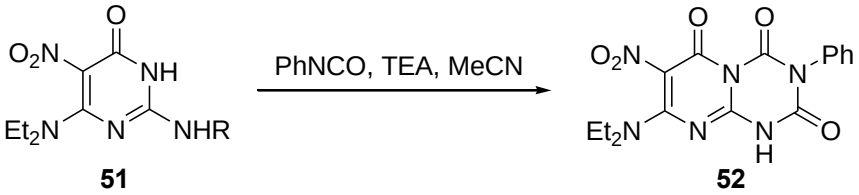
Pyrimidin-2-yl isocyanate (**45**) was also proposed as an intermediate in the reaction of pyrimidin-2-yliminotriphenylphosphorane (**47**) with phenyl isocyanate (Scheme 21).[24]



Scheme 21

However, competing synthetic pathway involving another intermediate - carbodiimide **48** increased complexity of the process. The preferred pathway, structure and composition of products were found to strongly depend on the reaction conditions. At ambient temperature, two products **46a** (minor) and **49** (major) were isolated from the reaction of **47** with excess of phenyl isocyanate. Their formation was explained *via* [4+2] cycloaddition of corresponding intermidiates **45** and **48** to the phenyl isocyanate molecule. Heating was found to reverse chemoselectivity of the process promoting formation of **46a**. Using only slight excess of phenyl isocyanate or its equimolar quantity and prolong reaction time resulted in the isolation of the carbodiimide **48** dimerization product **50**, mainly or even exclusively (when heating was applied). Interesting results were obtained in the hydrolysis study of **49**. After initial pyrimidine ring opening, the product was further hydrolyzed in presence of acid with the triazine ring cleavage and the pyrimidine ring recyclization.[25]

The reaction of substituted 2-aminopyrimidin-4-one and its acyl derivatives **51** with phenyl isocyanate in presence of base was reported[26] to provide pyrimido[1,2-*a*][1,3,5]triazin-2,4,6-trione **52** (Scheme 22).

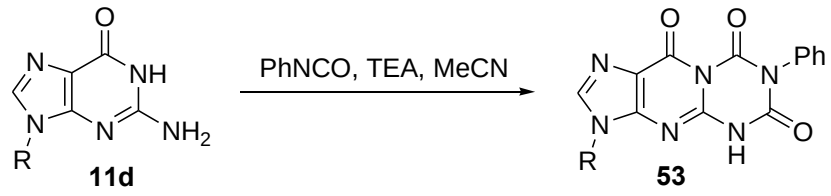


51 **52**

R = H, Ac, 4-MeOC$_6$H$_4$CO

Scheme 22

Analogously, treatment of *t*-butyldimethylsilyl protected deoxyguanosine (**11d**) with phenyl isocyanate resulted in the 1,3,5-ring closure leading to tricyclic nucleoside **53** (Scheme 23).[26]

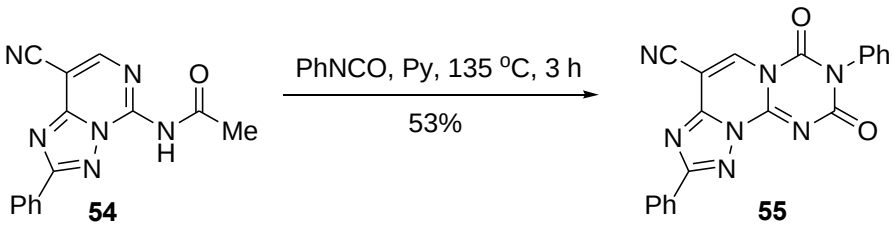


11d **53**

R = 3,5-di-*O*-TBDMS-deoxyribosyl

Scheme 23

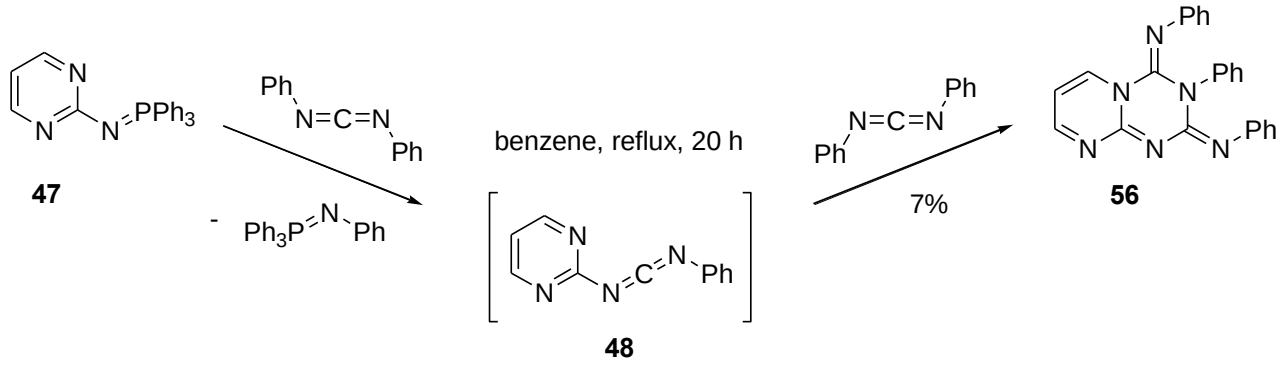
Another tricyclic 1,2,4-triazolo[1',5':3,4]pyrimido[1,2-*a*][1,3,5]triazine **55** was prepared in a similar manner from acetamide **54** and phenyl isocyanate (Scheme 24).[27]



54 **55**

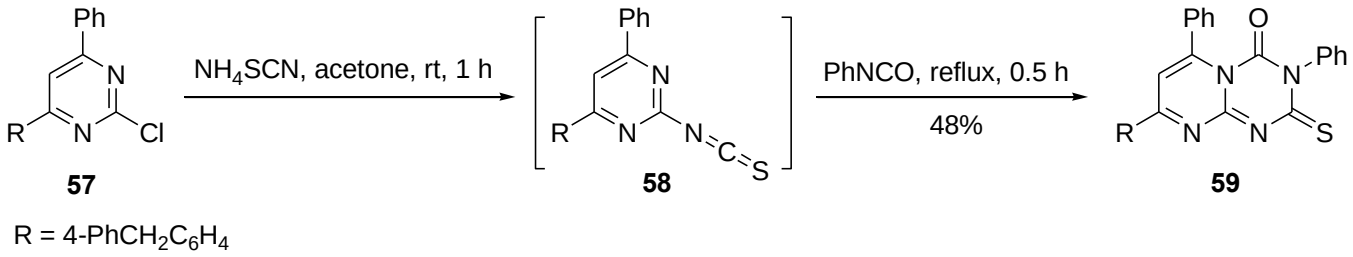
Scheme 24

The reaction of **47** with diphenylcarbodiimide provided **56** (Scheme 25).[28] The proposed reaction mechanism involved initial formation of carbodiimide **48** followed by the cycloaddition of another diphenylcarbodiimide molecule. The polymerization, observed during the reaction, was a reason for the low isolated yield of **56**.



Scheme 25

It was reported that treatment of 2-chloropyrimidine **57** with ammonium thiocyanate, followed by the [4+2] cycloaddition of intermediate isothiocyanate **58** and phenyl isocyanate resulted in the formation of 2-thioxopyrimido[1,2-*a*][1,3,5]triazin-4-one **59** (Scheme 26).[29] The regioselectivity of the cycloaddition step is questionable due to similar environment of the endocyclic pyrimidine nitrogen atoms of **57**, but no alternative structure was discussed in the paper.[29]

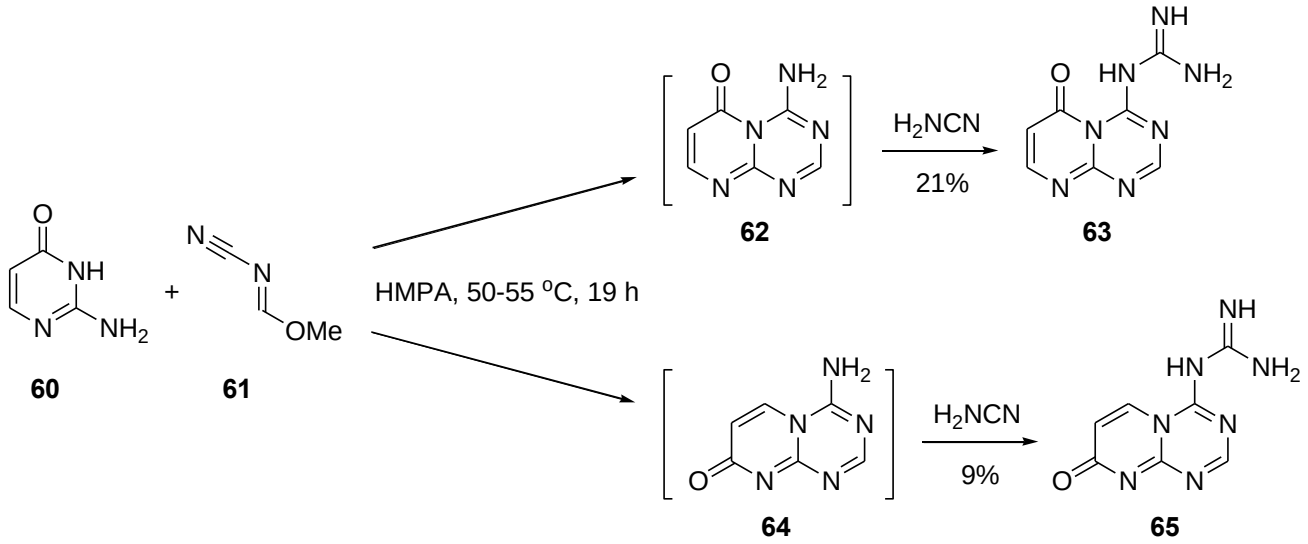


Scheme 26

2.3. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines *via* reactions of 2-aminopyrimidines with bielectrophilic C-N-C triatomic synthons

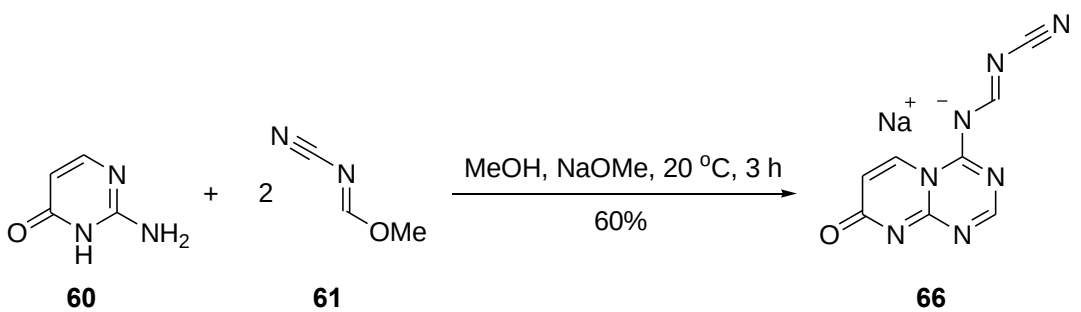
This synthetic approach allows convenient preparation of a variety of functionalized pyrimido[1,2-*a*][1,3,5]triazines from readily available 2-aminopyrimidines. The careful selection of the C-N-C triatomic synthons provides an opportunity for annelation of the 1,3,5-triazine ring with desirable substitution pattern. However, regiochemistry of the reaction should be always considered. Two endocyclic and one exocyclic nitrogen atoms are nucleophilic centers of 2-aminopyrimidines competing for two electophilic centers of the C-N-C synthons. Small changes in the reagent structure or variations of the reaction conditions may result in the preparation of any of four possible in general case isomeric pyrimido[1,2-*a*][1,3,5]triazines or their mixture. The investigations of the reactions of methyl *N*-cyanoformimidate (**61**) with 2-aminopyrimidines by Leonard's group[30-34] demonstrated complexity of this regioselectivity issue. Moreover, small variations in the reaction parameters also changed dramatically the chemoselectivity of the process.

Two isomeric pyrimido[1,2-*a*][1,3,5]triazines **63** and **65** were obtained in the ratio 2:1 upon treatment of isocytosine (**60**) with methyl *N*-cyanoformimidate (**61**) in hexamethylphosphoramide (HMPA) at 50-55 °C (Scheme 27).[30] The imidate group of **61** reacted with the exocyclic amino group of **60** followed by the 1,3,5-triazine ring closure to either of the endocyclic nitrogen atoms. However, the reaction products were different from expected amines **62** and **64**. It was suggested that cyanamide, produced in the reaction *via* an alternative process, reacted with formed as intermediates **62** and **64** to give corresponding guanidines **63** and **65**.



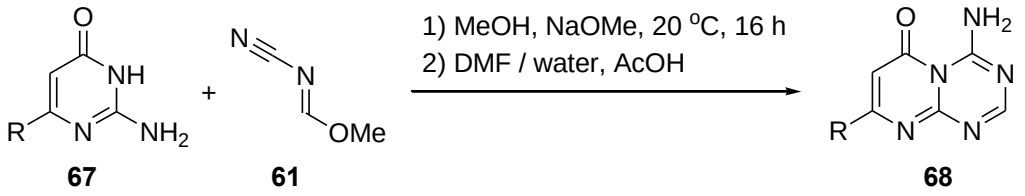
Scheme 27

Changing the reaction conditions made the direction of the 1,3,5-triazine ring closure selective, but amino group of intermediate **64**, formed after the initial annelation, underwent condensation with another molecule of **61** providing sodium salt **66** (Scheme 28).[31] Using lesser quantities of imidate **61** did not change the product composition, but just decrease the yield of **66**. The side chain of **66** was cleaved and structure of resulted 4-aminopyrimido[1,2-*a*][1,3,5]triazin-8-one (**64**) was determined using X-ray diffraction analysis of its triflate salt.



Scheme 28

The opposite regiochemistry of the 1,3,5-triazine ring annelation was observed when 6-substituted isocytosine analogues **67** were treated with **61** (Scheme 29).[31] Furthermore, even with a substantial excess of imidate **61** only amines **68** were isolated from the reaction.

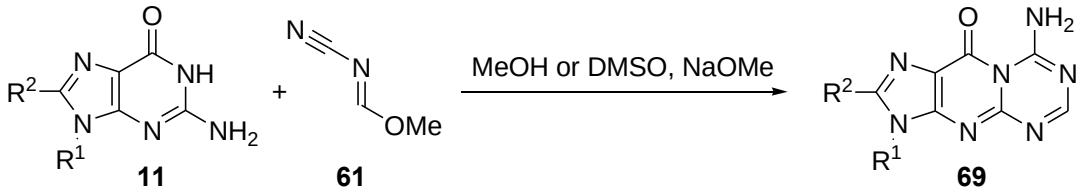


67 **61** **68**

R = Me, 79% (**68a**); N(Me)Bn, 76% (**68b**)

Scheme 29

Similarly, guanine nucleosides and their analogues (**11**) reacted with **61** affording fused tricyclic compounds **69** (Scheme 30).[32-34] The structure of **69** was confirmed by X-ray diffraction analysis of **69c**[32,33] and deoxyguanosine derivative **69f**.[34] The N^{15} NMR spectroscopic study, determination of pKa, and assessment of hydrolytic stability of the glycosidic bond of guanosine derivative **69d** were also performed.[35]



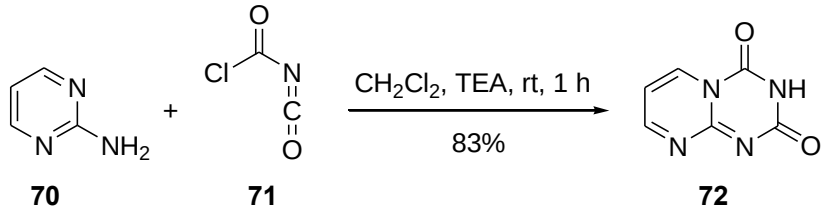
11 **61** **69**

R^1 = $HOCH_2CH_2OCH_2$, R^2 = H, 86% (**69a**);
R^1 = Bn, R^2 = H, 80% (**69b**); Br, 73% (**69c**);
R^1 = ribosyl, R^2 = H, 39% (**69d**); Br, 35% (**69e**);
R^1 = deoxyribosyl, R^2 = H, 34% (**69f**)

Scheme 30

Isocyanates bearing at the nitrogen atom another reactive electrophilic group found an application as C-N-C triatomic synthons allowing annelation of 1,3,5-triazine ring with at least one carbonyl group. The nature of the electrophilic group attached to the isocyanate determines other types of substitutuents on the created triazine ring as well as governs regioselectivity of the ring closure.

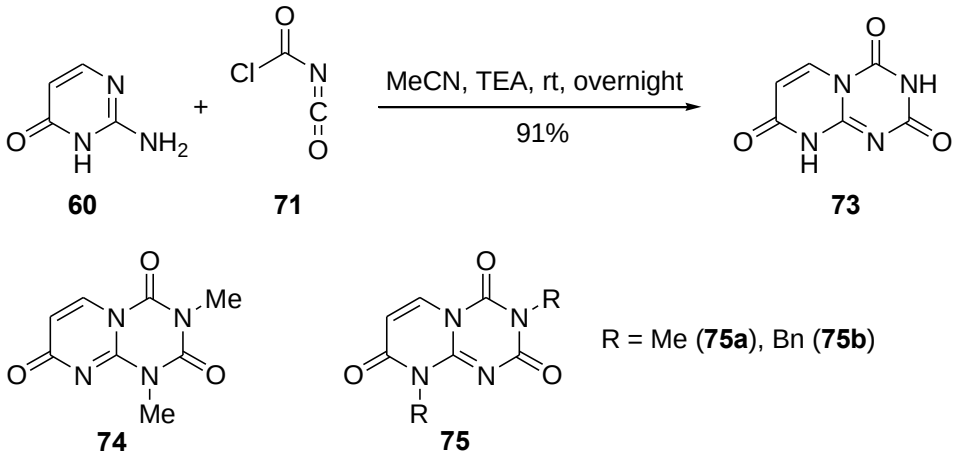
Chlorocarbonyl isocyanate (**71**) is the most popular reagent for the annelation of 1,3,5-triazin-2,4-dione to 2-aminopyrimidines. Pyrimido[1,2-*a*][1,3,5]triazin-2,4-dione (**72**) was conveniently prepared by the treatment of 2-aminopyrimidine (**70**) with **71** in presence of base at ambient temperature (Scheme 31).[36]



70 **71** **72**

Scheme 31

Isocytosine (**60**) reacted with **71** affording pyrimido[1,2-*a*][1,3,5]triazin-2,4,8-trione (**73**) in 91% yield (Scheme 32).[37] The product (**73**) was further alkylated and X-ray crystallographic study of methyl and benzyl derivatives **74** and **75** was used to confirm the regiochemistry of the ring closure.

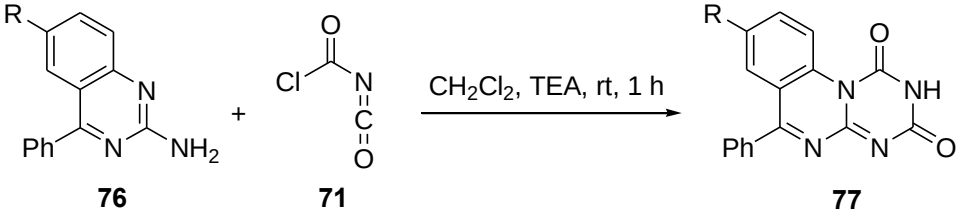


60 **71** **73**

74 **75**

Scheme 32

Analogously, the 1,3,5-triazin-2,4-dione was annelated to 2-amino-4-phenylquinazolines (**76**) with the ring closure to N-1 of the quinazoline nucleus (Scheme 33).[36] The theoretically possible regioisomeric structure, alternative to **77**, was not mentioned.

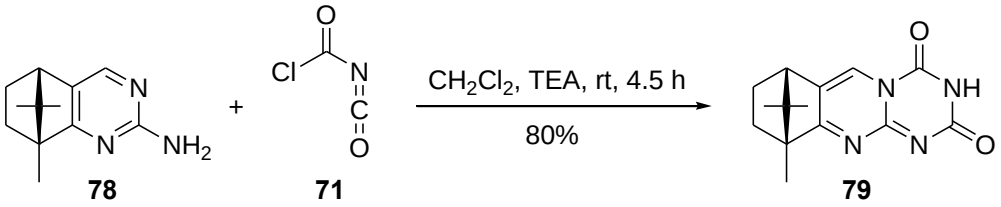


76 **71** **77**

R = H, 86% (**77a**); Cl, 91% (**77b**)

Scheme 33

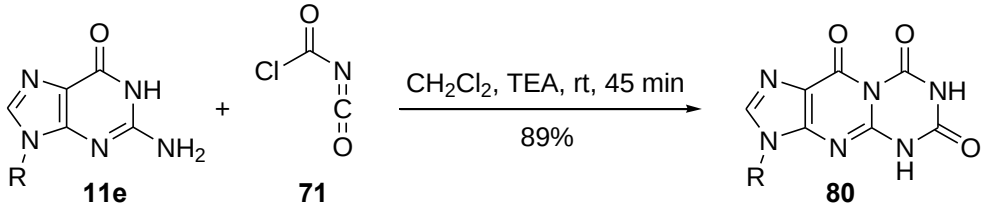
Compound **79**, prepared by the treatment of **78** with chlorocarbonyl isocyanate (**71**) (Scheme 34), was shown to possess central nervous stimulant activity comparable with penthylenetetrazole.[38]



78 71 79

Scheme 34

Similarly, benzoyl protected guanosine **11e** was smoothly converted to **80** (Scheme 35).[39] However, deprotection attempts were unsuccessful and resulted in the triazine ring cleavage.

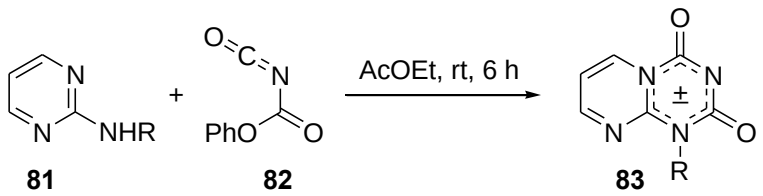


11e **71** **80**

R = 2,3,5-tri-*O*-benzoylribosyl

Scheme 35

Greco and Gala[40] reported the reaction of 2-alkylaminopyrimidines (**81**) with phenoxycarbonyl isocyanate (**82**) affording corresponding mesoionic 1-alkyl substituted pyrimido[1,2-*a*][1,3,5]triazin-2,4-diones (**83**) (Scheme 36).

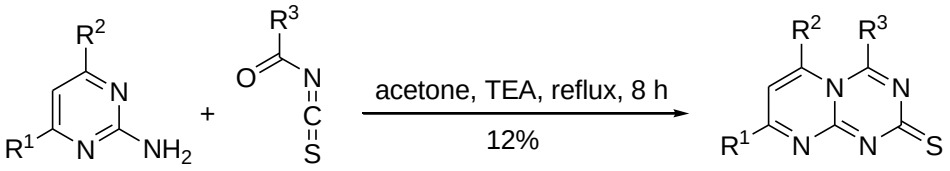


81 **82** **83**

R = Me, 88% (**83a**); Et, 60% (**83b**)

Scheme 36

The condensation of 4,6-diaryl substituted 2-aminopyrimidine **84** and aroyl isothiocyanate **85** (Scheme 37), in principle, might result in the formation of four regioisomeric pyrimido[1,2-*a*][1,3,5]triazines depending on the regioselectivity of the process. However, the isolation of one product **86** was reported[41] with no conclusive evidence supporting this structure.



84 **85** **86**

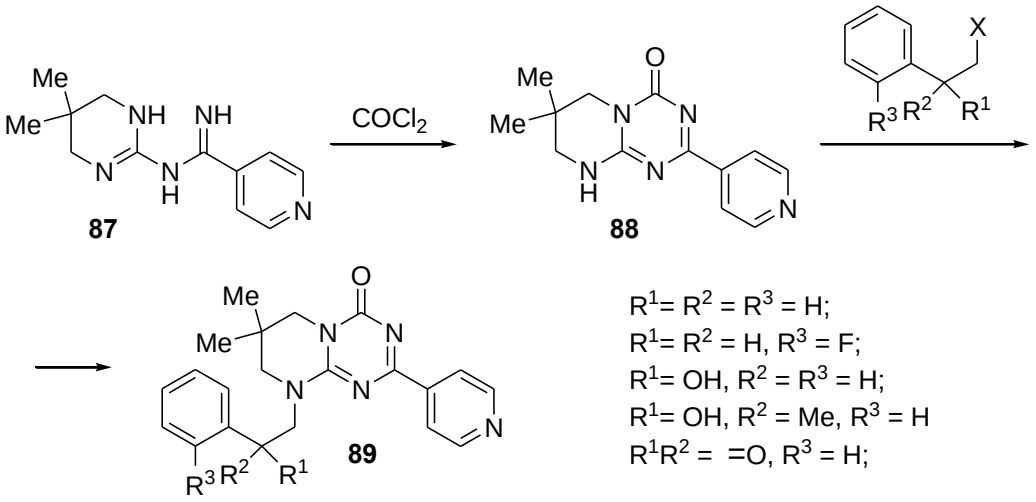
R^1 = 4-$MeOC_6H_4$, R^2 = 3,4,5-$(MeO)_3C_6H_2$, R^3 = 4-$NO_2C_6H_4$

Scheme 37

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

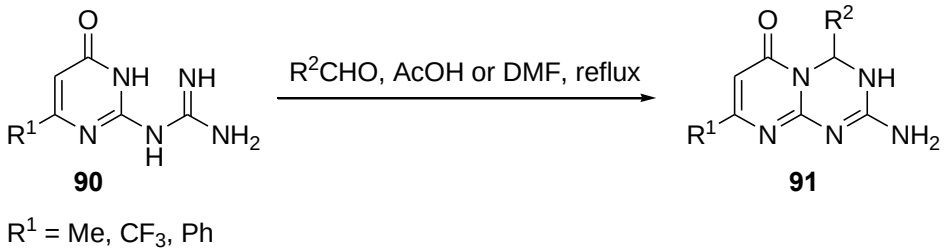
This approach for the 1,3,5-triazine ring annelation was applied for pyrimidines with various functional groups including amidines, guanidines, ureas, and thioureas *etc*. Diverse choice of one-carbon inserting reagents opens an avenue for introducing different substituents (*e.g.* alkyl, aryl, hetaryl, amino, carbonyl, thiocarbonyl groups) into position 4 of the 1,3,5-triazine ring. The regioselectivity of the ring closure remains an important issue in some of the reactions utilizing this synthetic approach.

Pyrimido[1,2-*a*][1,3,5]triazines **89**, claimed[42] as GSK3-β inhibitors with potential for the treatment of neurodegenerative diseases, were prepared by the ring closure carbonylation of amidine **87** with phosgene followed by the alkylation of intermediate **88** (Scheme 38). However, no details of the synthetic procedure were provided.



Scheme 38

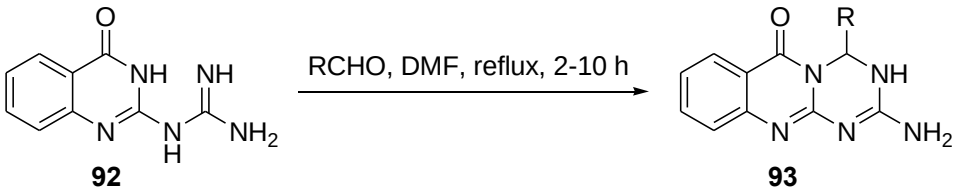
The thermal cyclocondensation of guanidines **90** with aldehydes was used for the synthesis of **91** (Scheme 39).[43,44] The X-ray diffraction study[44] of **91** (R^1 = CF_3, R^2 = 4-BrC_6H_4) proved the side of the ring closure.



R^1 = Me, CF_3, Ph

Scheme 39

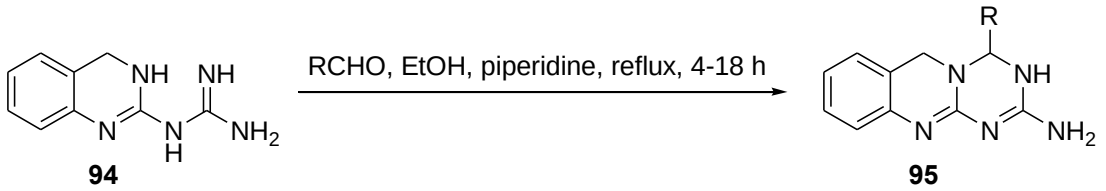
Similarly, the synthesis of benzofused tricyclic analogues **93** was achieved *via* the 1,3,5-triazine ring annelation to the side *b* of quinazolinone **92** using a variety of aldehydes (Scheme 40).[45]



R = Ph, 61% (**93a**); 4-MeC_6H_4, 52% (**93b**); 4-$MeOC_6H_4$, 55% (**93c**); 4-FC_6H_4, 62% (**93d**); 4-ClC_6H_4, 63% (**93e**); 4-BrC_6H_4, 74% (**93f**); 2-Furyl, 60% (**93g**); 2-Thienyl, 58% (**93h**); 3-Py, 82% (**93i**)

Scheme 40

The same regiochemistry was observed in the synthesis of similar compounds **95** (Scheme 41).[46] The base catalyzed cyclocondensation of 3,4-dihydroquinazolin-2-yl guanidine (**94**) with aldehydes resulted in the 1,3,5-ring closure at the N-3 atom of **94** that was confirmed by the 2D NOESY NMR spectral data of **95**. Some of products **95** showed activity against lung (A549) and breast (MDA-MB-231) cancer cell lines. Thus, **95f** demonstrated IC_{50} values of 17 and 15 μM against lung and breast cancer cells, respectively.

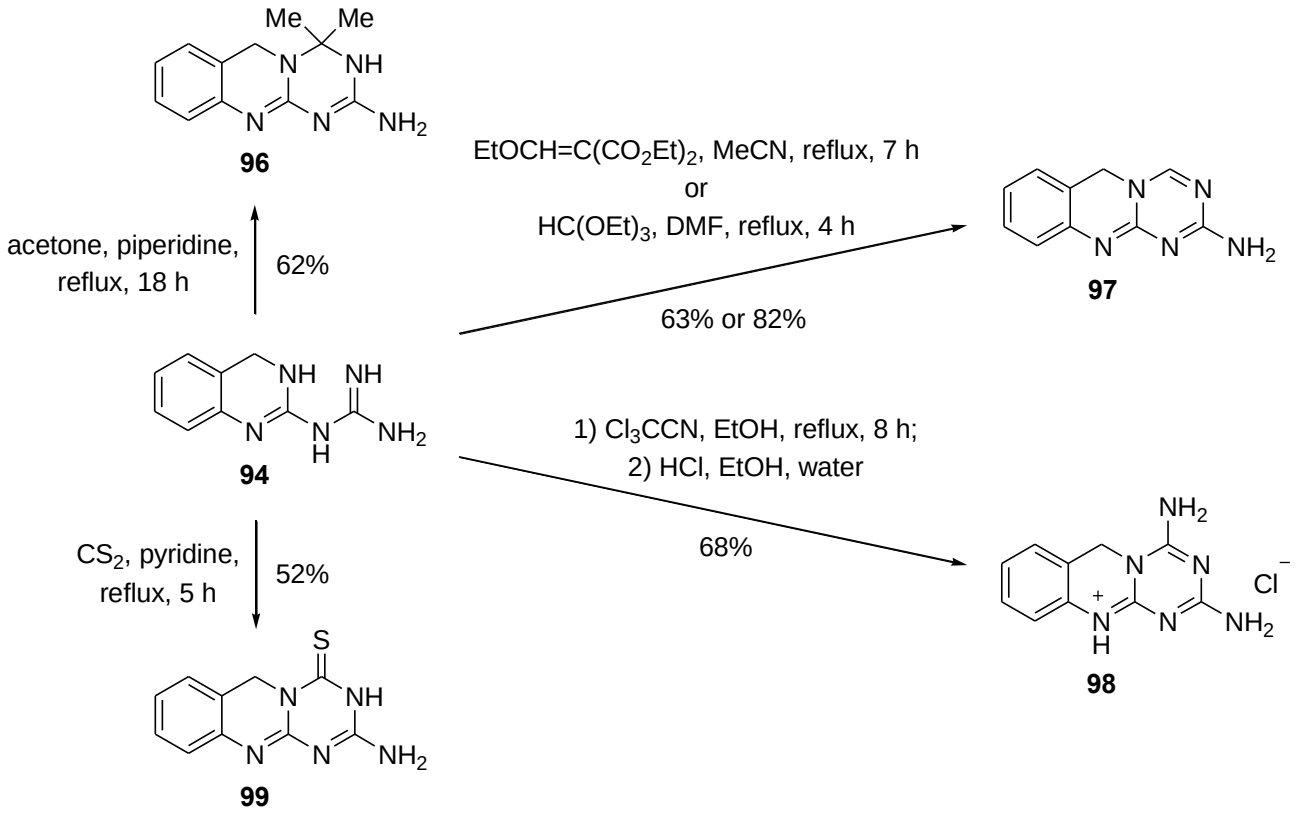


R = Ph, 85% (**95a**); 4-MeC_6H_4, 72% (**95b**); 4-$MeOC_6H_4$, 58% (**95c**); 4-$(Me_2N)C_6H_4$, 75% (**95d**); 4-ClC_6H_4, 84% (**95e**); 4-BrC_6H_4, 87% (**95f**); 2-Thienyl, 82% (**95g**); 3-Py, 77% (**95h**)

Scheme 41

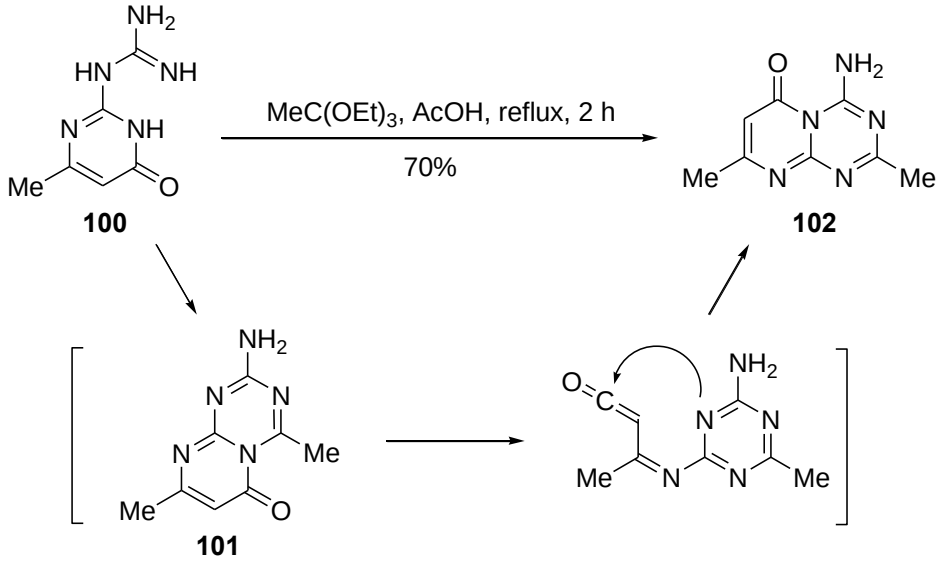
A variety of one-carbon inserting reagents were applied to construct appropriately substituted 1,3,5-triazine ring on the 3,4-dihydroquinazolin-2-yl guanidine (**94**) skeleton (Scheme 42).[46]

Gem-dimethyl substituted compound **96** was prepared using acetone as one-carbon inserting reagent. The condensations of **94** with diethyl ethoxymethylenemalonate or triethyl orthoformate afforded the same product 2-amino-6*H*-1,3,5-triazino[2,1-*b*]quinazoline (**97**). The 2,4-diamino-1,3,5-triazine ring was annelated to **94** *via* the reaction with trichloroacetoniltile providing **98**. The synthesis of **99** was successfully achieved by the ring closure thiocarbonylation of **94** with carbon disulfide.



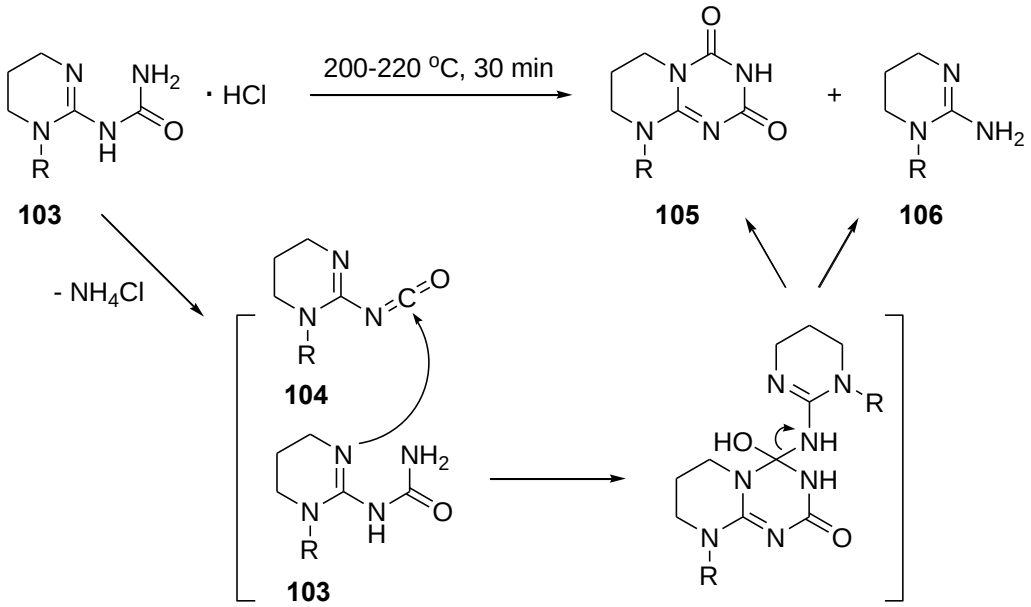
Scheme 42

Unexpected product was obtained when guanidine **100** was treated with triethyl orthoacetate (Scheme 43).[47] Instead of expected 2-amino-4,8-dimethylpyrimido[1,2-*a*][1,3,5]triazin-6-one (**101**), its 4-amino-2,8-dimethyl substituted isomer **102** was isolated. The formation of **102** can be rationalized by the rearrangement of **101** under the reaction condition *via* the pyrimidine ring opening of **101** and subsequent recyclization to another nitrogen atom of the 1,3,5-triazine nucleus. The strong intramolecular hydrogen bonding stabilizes rearranged product **102**.



Scheme 43

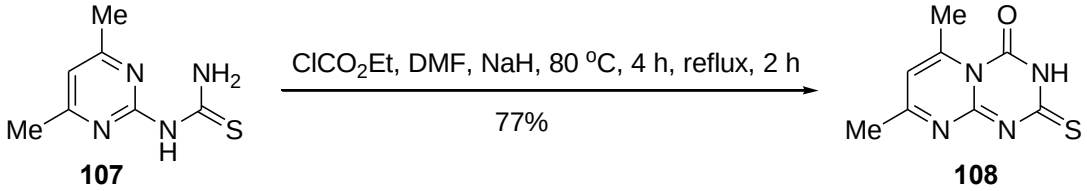
The thermolysis of ureas **103** was reported to afford pyrimido[1,2-*a*][1,3,5]triazin-2,4-diones **105** along with decarbamoylation products **106** (Scheme 44).[48] Although the mechanism of the reaction was not investigated and discussed, it might be assumed that both products formed in the concerted process, presumably *via* the corresponding isocyanate **104** intermediacy.



R = Bn, 29% (**105a**) + 43% (**106a**); Ph_2CH, 25% (**105b**) + 38% (**106b**)

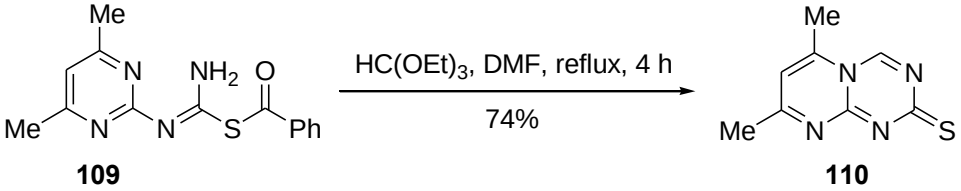
Scheme 44

The synthesis of 6,8-dimethyl-2-thioxopyrimido[1,2-*a*][1,3,5]triazin-4-one (**108**) was performed *via* the ring closure carbonylation of thiourea **107** using ethyl chloroformate (Scheme 45).[49]



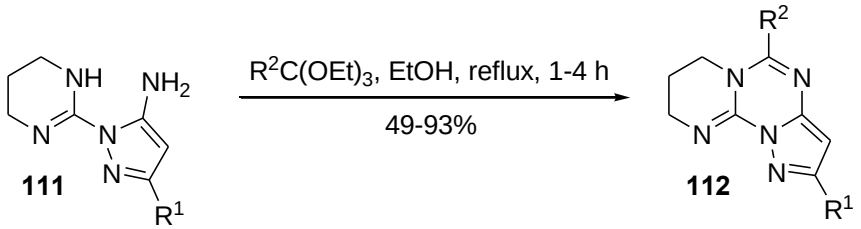
Scheme 45

In the condensation with triethyl orthoformate, the *S*-benzoyl substituted isothiourea **109**, derived from **107**, was reported[49] to produce 6,8-dimethylpyrimido[1,2-*a*][1,3,5]triazin-2-thione (**110**) (Scheme 46). Both **108** and **110** demonstrated antibacterial activity against *Klebsiella pneumoniae*.



Scheme 46

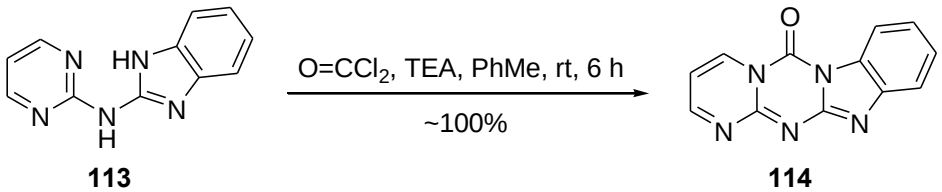
Several triethyl orthoesters were used as one-carbon inserting reagents for the construction of 1,3,5-triazine ring connecting pyrimidine and pyrazole rings of **111** and therefore converting **111** into tricyclic compounds **112** (Scheme 47).[50]



R^1 = Me, Ph, 4-MeC_6H_4; R^2 = H, Me, Et, Ph

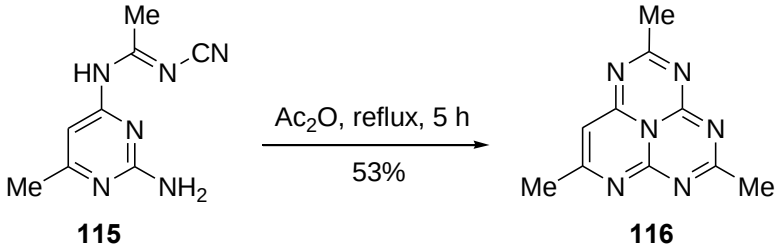
Scheme 47

The treatment with phosgene was used to introduce a carbonyl group connecting pyrimidine and benzimidazole nitrogen atoms of 2-pyrimidin-2-ylaminobenzimidazole (**113**) (Scheme 48).[51] Tetracyclic product **114** was formed in almost quantitative yield.



Scheme 48

Pentaazacyclazine **116** was synthesized by the condensation of **115** with acetic anhydrate (Scheme 49).[52] Two 1,3,5-triazine rings were annelated *via* the three-bond formation cyclization. Acetic anhydride supplied one carbon atom to the 1,3,5-triazine ring having a [1,2-*a*] junction with the pyrimidine nucleus.

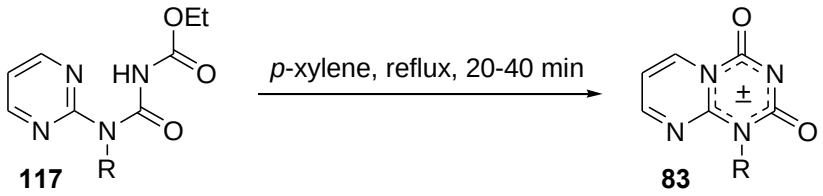


115 **116**

Scheme 49

2.5. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines *via* intramolecular cyclization of substituted pyrimidines

The thermal cyclization of **117**, prepared by the reaction of 2-aminopyrimidines **81** with ethoxycarbonyl isocyanate (*cf.* Scheme 36), resulted in the formation of mesoionic compounds **83** (Scheme 50).[40]

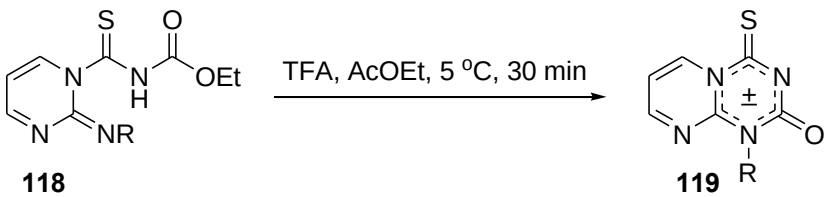


117 **83**

R = Me, 35% (**83a**); Et, 27% (**83b**)

Scheme 50

The addition of ethoxycarbonyl isothiocyanate to the endocyclic nitrogen atom of 2-aminopyrimidines **81** gave **118**, which underwent cyclocondensation in presence of trifluoroacetic acid affording mesoionic compounds **119** (Scheme 51).[40]

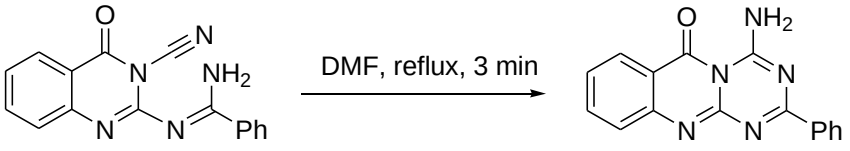


118 **119**

R = Me, 48% (**119a**); Et, 20% (**119b**)

Scheme 51

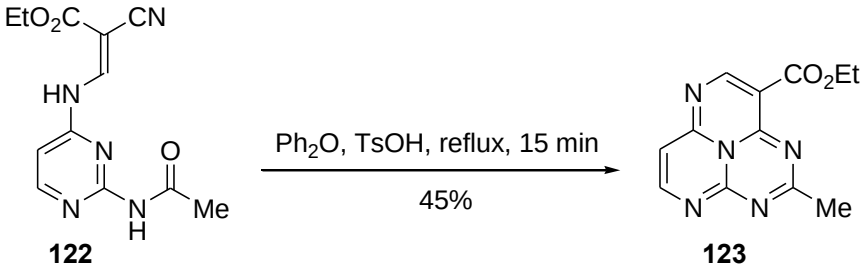
A partial conversion of **120** to **121a** was observed in the attempt of crystallization of **120** from methanol. The 1,3,5-triazine ring closure was successfully completed by short heating **120** in DMF (Scheme 52).[53]



120 **121a**

Scheme 52

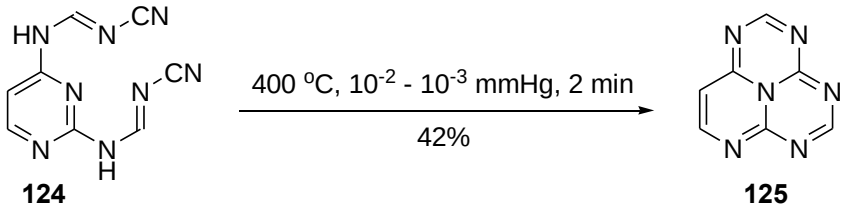
The pyrimidine and 1,3,5-triazine ring closure with three-bond formation affording tetraazacyclazine **123** occurred when pyrimidine **122** was heated in diphenyl ether in the presence of tosylic acid (Scheme 53).[54]



122 **123**

Scheme 53

The sublimation of 1,3,4,6,7-pentaazacycl[3.3.3]azine (**125**) was achieved as a result of short vacuum pyrolysis of 2,4-bis(*N*′-cyano-*N*-formamidino)pyrimidine (**124**) (Scheme 54).[55] The ionization potential of **125** was assessed experimentally and calculated along with the electron distribution and reactivity indexes.



124 **125**

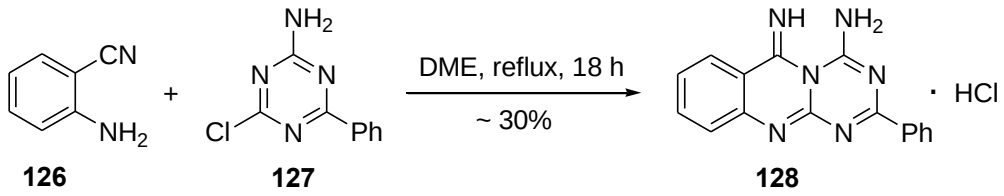
Scheme 54

3. SYNTHESIS OF PYRIMIDO[1,2-*a*][1,3,5]TRIAZINES BY ANNELATION OF THE PYRIMIDINE RING ONTO A 1,3,5-TRIAZINE SCAFFOLD

The first synthesis of pyrimido[1,2-*a*][1,3,5]triazines was performed by the annelation of the pyrimidine ring to 2,4-diamino-1,3,5-triazine (**1**) (*vide supra* Scheme 1).[2] Further exploration of this general approach resulted in the development of several effective synthetic methods summarized below.

3.1. Synthesis of 1,3,5-triazino[2,1-*b*]quinazolines (benzofused pyrimido[1,2-*a*][1,3,5]triazines) *via* reactions of chloro substituted 1,3,5-triazines with anthranilic acid derivatives

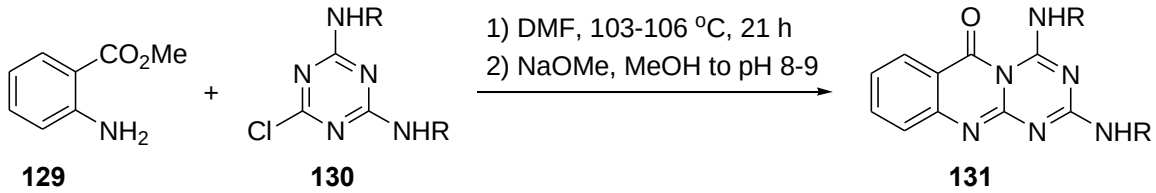
This group of reaction is based on the nucleophilic substitution of reactive chlorine atom on carbon atom of 1,3,5-triazines by amino group of anthranilic acid derivatives followed by the pyrimidine ring closure to the endocyclic nitrogen atom of the 1,3,5-triazine core. Thus, the reaction of anthranilonitrile (**126**) with 2-amino-4-chloro-6-phenyl-1,3,5-triazine (**127**) gave 1,3,5-triazino[2,1-*b*]quinazoline **128** (Scheme 55).[53]



126 **127** **128**

Scheme 55

The synthesis of 2,4-diamino-1,3,5-triazino[2,1-*b*]quinazolin-6-ones **131** was performed *via* the condensation of methyl anthranilate (**129**) and 2,4-diamino-6-chloro-1,3,5-triazines **130** (Scheme 56).[53]

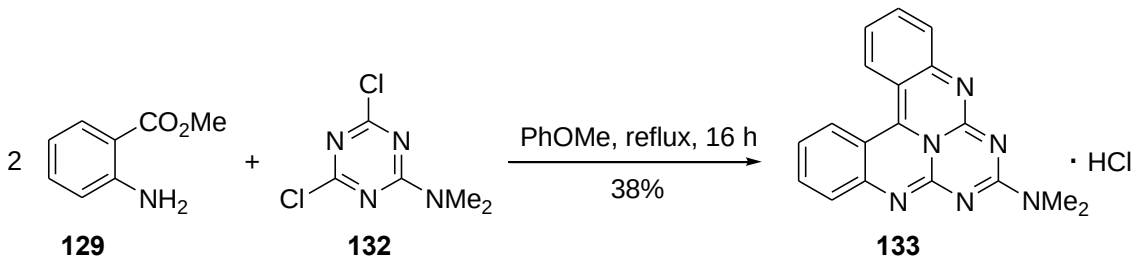


129 **130** **131**

R = Me, 28% (**131a**); Et, 22% (**131b**); Bn, 23% (**131c**)

Scheme 56

The formation of **133** having 1,3,5-triazine ring fused with two quinazoline nuclei was claimed[56] to take place when 4,6-dichloro-2-dimethylamino-1,3,5-triazine (**132**) was heated in anisole with two equivalents of methyl anthranilate (**129**) (Scheme 57). The reaction yield was 38%, however subsequent overnight heating of the reaction residue in acetic acid allowed additional isolation of 33% of **133** (*cf.* Scheme 69).

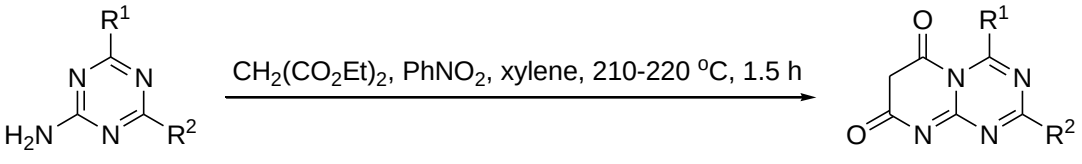


129 **132** **133**

Scheme 57

3.2. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines *via* reactions of 2-amino-1,3,5-triazines with bielectrophilic C-C-C triatomic synthons

Similarly to the firs report on the synthesis of pyrimido[1,2-*a*][1,3,5]triazines (*vide supra* Scheme 1), all reactions described in this section utilized derivatives of malonic acid for the annelation of pyrimidine ring to 2-amino-1,3,5-triazines. The reaction of melamine (**134**, $R^1 = R^2 = NH_2$) and its alkyl substituted derivatives with diethyl malonate was used for the preparation of 2,4-diamino-7*H*-pyrimido[1,2-*a*][1,3,5]triazin-6,8-diones **135** (Scheme 58), which were claimed[57] to be useful as insecticides. The yield in case of **135** with $R^1 = NH_2$, $R^2 = NMe_2$ was good (93%); no data for other **135** were reported.

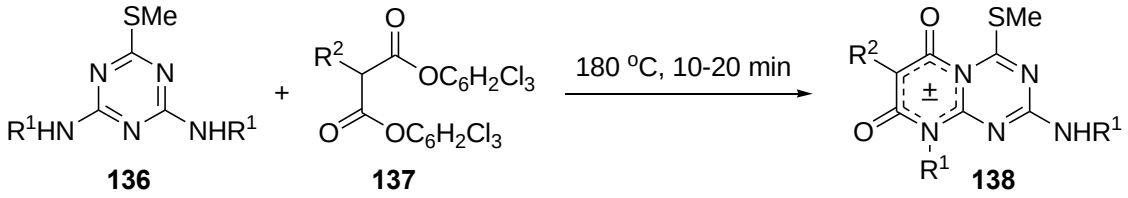


134 **135**

$R^1 = NH_2$, $R^2 = NH_2$, Me_2N, Et_2N, Morpholin-4-yl; $R^1 = R^2 = Me_2N$

Scheme 58

The fusion of **136** with 2,4,6-trichlorophenyl 2-alkylmalonates (**137**) at 180 °C resulted in the formation of mesoionic pyrimido[1,2-*a*][1,3,5]triazines **138** (Scheme 59).[58] Although the annelation of pyrimidine ring might resulted from the ring closure to either of two nonequivalent endocyclic nitrogen atoms of triazines **136**, regioselectivity of the process was not discussed and no unequivocal data excluding a structure regioisomeric to **138** were provided. Moreover, the observed low field shift of the amino group signals (12.62-12.73 ppm) of **138** can be attributed to intramolecular hydrogen bonding with neighboring carbonyl group in the isomeric pyrimido[1,2-*a*][1,3,5]triazine structure.

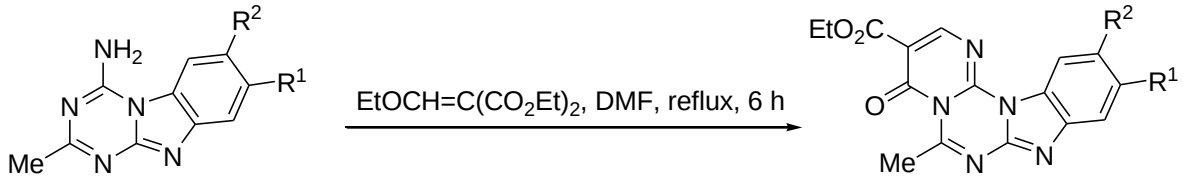


136 **137** **138**

R^1 = Et, R^2 = Et, 92% (**138a**); Bu, 95% (**138b**); Bn, 76% (**138c**);
R^1 = *i*-Pr, R^2 = Et, 62% (**138d**); Bn, 68% (**138e**).

Scheme 59

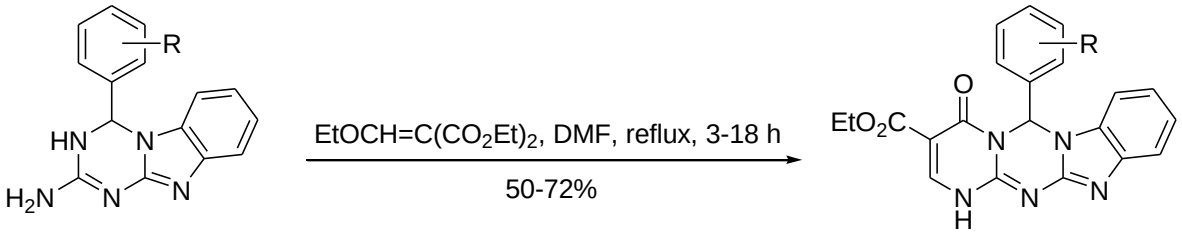
Tetracyclic pyrimido[1,2-*a*][1,3,5]triazines fused with benzimidazole nucleus, compounds **140**[59] and **142**[60] were synthesized *via* the annelation of pyrimidine ring to corresponding amino substituted 1,3,5-triazino[1,2-*a*]benzimidazoles **139** and **141** using diethyl ethoxymethylenemalonate (Schemes 60 and 61). The regioselectivity of the later reaction was assigned using a number of spectroscopic techniques and parameters.



139 **140**

R^1 = H, R^2 = H, 78% (**140a**); Cl, 68% (**140b**); PhCO, 79% (**140c**); R^1 = R^2 = Me, 80% (**140d**)

Scheme 60



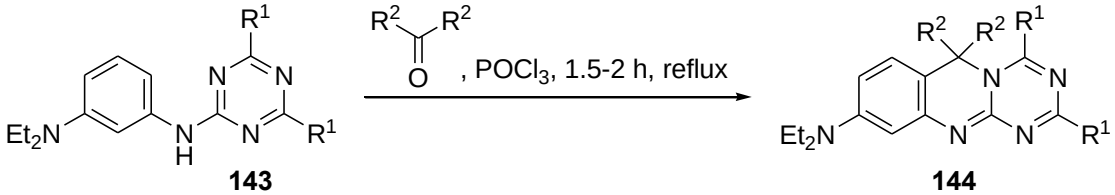
141 **142**

R = H, 2-Me, 3-Me, 4-Me, 2-MeO, 3-MeO, 4-MeO, 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br

Scheme 61

3.3. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines *via* pyrimidine ring annelation on 2-substituted 1,3,5-triazines using one-carbon inserting reagents

This type of the pyrimido[1,2-*a*][1,3,5]triazine synthesis is represented by the condensation of triazine **143** with phosphoryl chloride activated Michler's ketone affording **144** (Scheme 62) useful as blue dyes.[61]



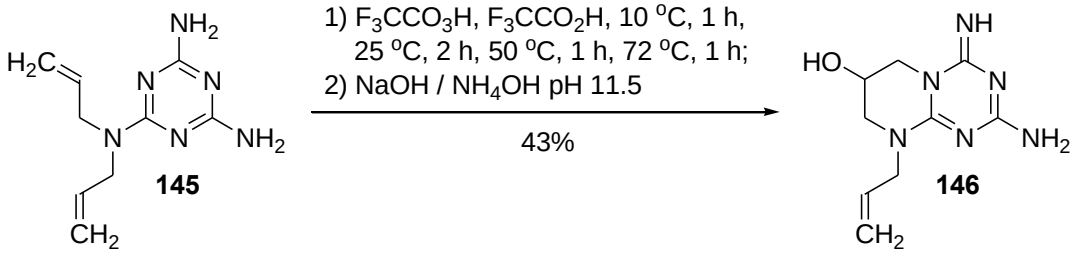
143 **144**

R^1 = MeO, Me_2N, Piperidin-1-yl, Morpholin-4-yl, R^2 = 4-$(Me_2N)C_6H_4$

Scheme 62

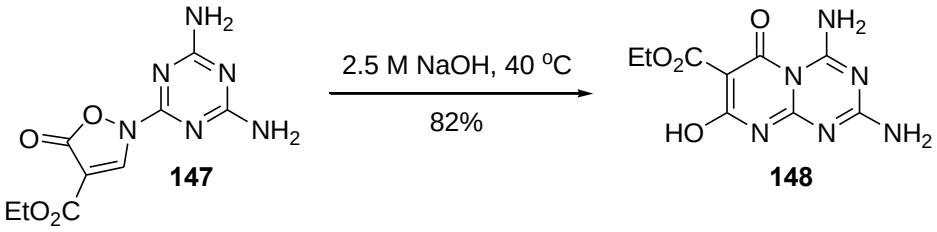
3.4. Synthesis of pyrimido[1,2-*a*][1,3,5]triazines *via* intramolecular cyclization of substituted 1,3,5-triazines

The intramolecular cyclization of N^2,N^2-diallyl substituted melamine (**145**) upon treatment with trifluoroperacetic acid resulted in the tetrahydropyrimidine annelation providing **146** (Scheme 63).[62] The analogues of **146** with alkyl group other than allyl were also claimed to be preparable by this method from the corresponding N^2-alkyl-N^2-allylmelamines. The central nervous system depressant activity was mentioned for **146**, but no details were provided.



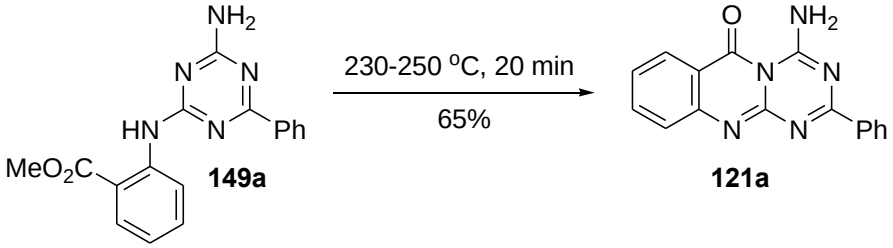
Scheme 63

The base-induced isoxazolone ring opening of **147** followed by the intramolecular cyclization with the pyrimidine ring formation was reported to give **148** (Scheme 64).[63] The rearrangement appeared to be general and proceed *via* similar mechanism[64] for various related heterocyclic molecules with the isoxazolone moiety.



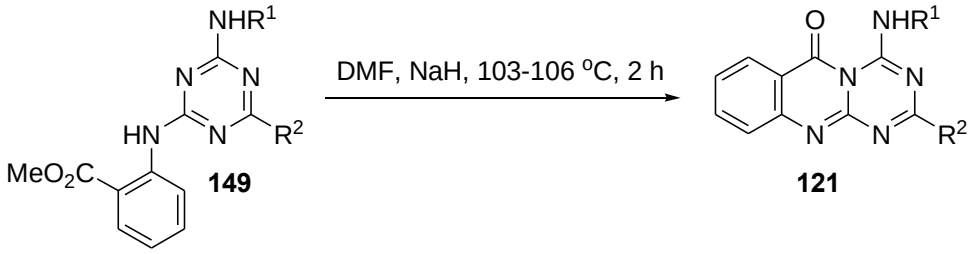
Scheme 64

A number of intramolecular cyclizations based on the reactions of anthranilic acid derivatives with 1,3,5-triazine ring attached to the amino group has been described in the literature. This approach was efficiently used for the preparation of heterocyclic systems of different complexity. Thus, heating **149a** above its melting point allowed preparation of 4-amino-2-phenyl-1,3,5-triazino[2,1-*b*]quinazolin-6-one (**121a**) (Scheme 65).[53,65]



Scheme 65

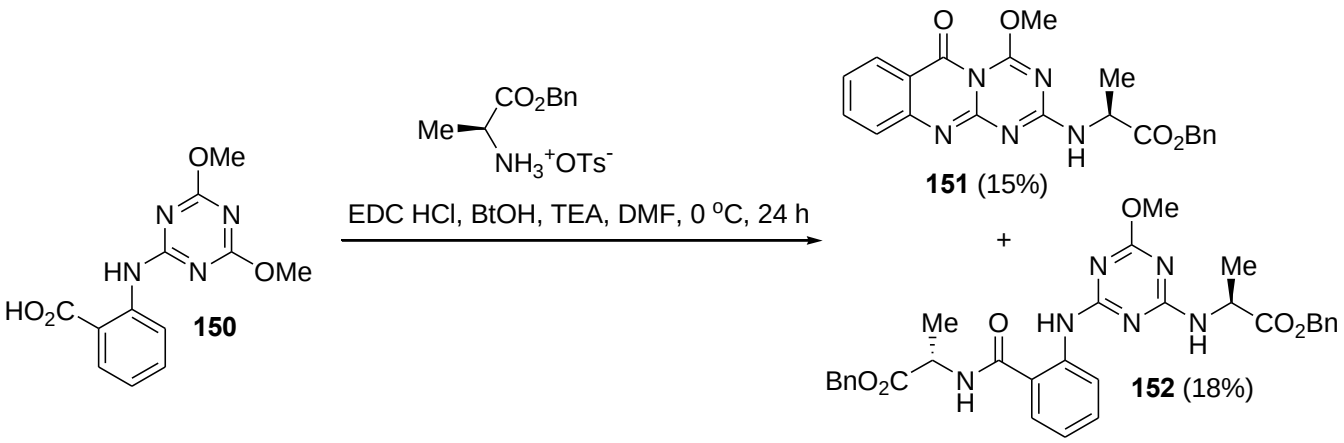
More efficient synthesis of **121a** and its analogues was achieved by the treatment of **149** with sodium hydrate in DMF (Scheme 66).[53]



R^1 = H, R^2 = Ph, 82% (**121a**); R^2 = Me_2N, 65% (**121b**); R^1 = Me, R^2 = Me_2N, 84% (**121c**); R^1 = Ph, R^2 = PhNH, 26% (**121d**); R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4NH$, 23% (**121e**)

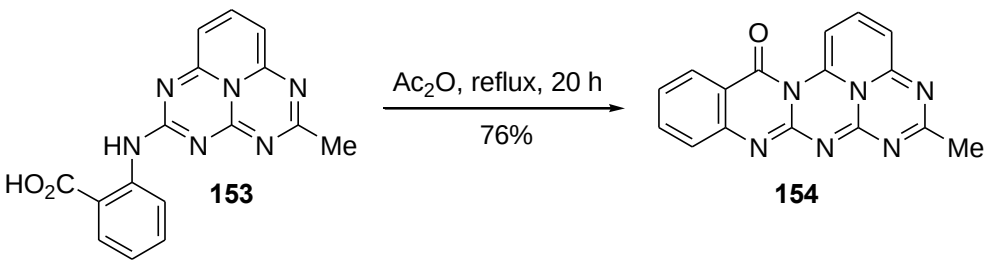
Scheme 66

In the attempt to convert the carboxylic group of anthranilic acid derivative **150** into the amide with tosylate of D-alanine benzyl ester, one of the methoxy groups of **150** underwent nucleophilic substitution while the activated carboxylic group of **150** participated in two processes: the 1,3,5-triazine ring closure affording tricyclic **151** and the expected amide formation providing **152** (Scheme 67).[66]



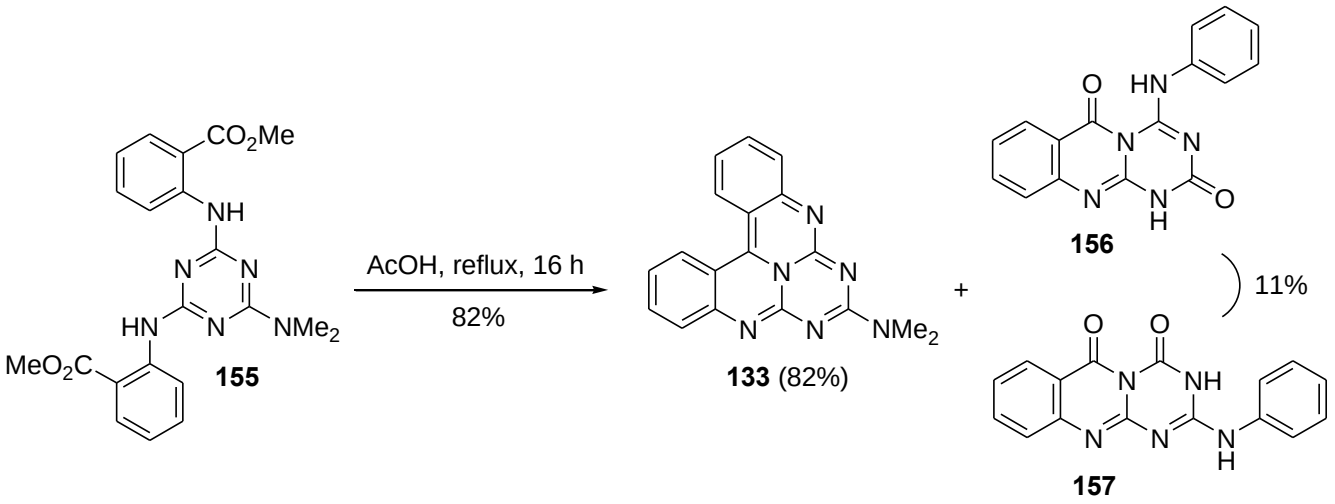
Scheme 67

The cyclization of cyclazine **153** was achieved by heating in acetic anhydrate (Scheme 68).[67] The reaction was found to give only one polycyclic product **154**, which was distinguished from its possible regioisomer on the basis of spectral data.



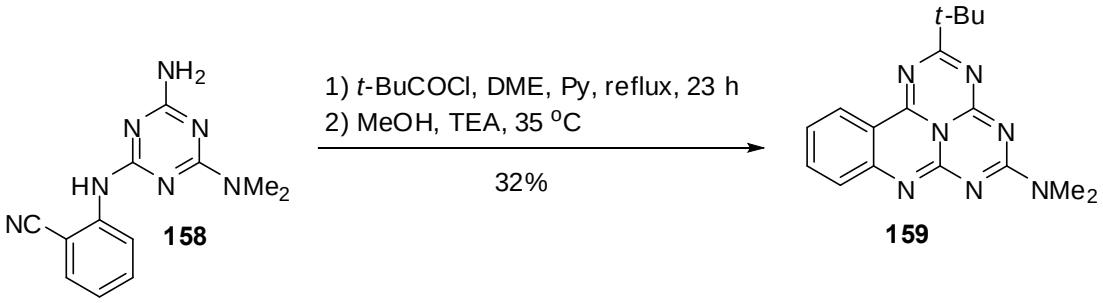
Scheme 68

The decarboxylation together with the intramolecular cyclization took place when triazine **155** was heated in acetic acid (Scheme 69). Pentacyclic **133** was obtained[56] from the reaction along with 11% of the byproduct, to which structure **156** or **157** was proposed.[68] The separation of **133** and 1,3,5-triazino[2,1-*b*]quinazoline (**156** / **157**) was performed using different solubility of the products.



Scheme 69

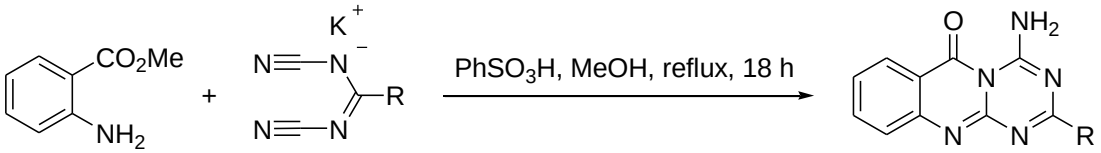
The quinazoline and triazine rings were formed when triazine **158** was treated with pivaloyl chloride affording tetracyclic structure **159** (Scheme 70).[69]



Scheme 70

4. SYNTHESIS OF PYRIMIDO[1,2-*a*][1,3,5]TRIAZINES *VIA* FORMATION OF PYRIMIDINE AND 1,3,5-TRIAZINE RINGS IN ONE REACTION

A few methods have been developed for the construction of both pyrimidine and 1,3,5-triazine rings of the pyrimido[1,2-*a*][1,3,5]triazine system in one reaction. The reaction of methyl anthranilate (**129**) with potassium *N,N*^{1}-dicyanobenzamidine and its analogues (**160**) resulted in the formation of two new rings affording 2-substituted 4-amino-1,3,5-triazino[2,1-*b*]quinazolin-6-ones **121** (Scheme 71).[53,65]

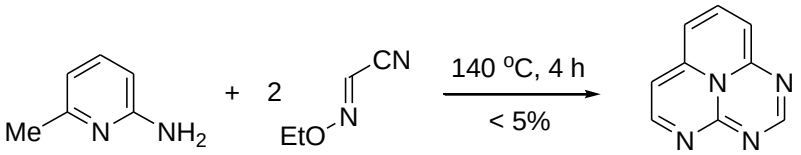


129 **160** **121**

R = Ph, 51% (**121a**); 4-ClC_6H_4, 41% (**121f**); 4-MeC_6H_4, 55% (**121g**); NH_2, 40% (**121h**)

Scheme 71

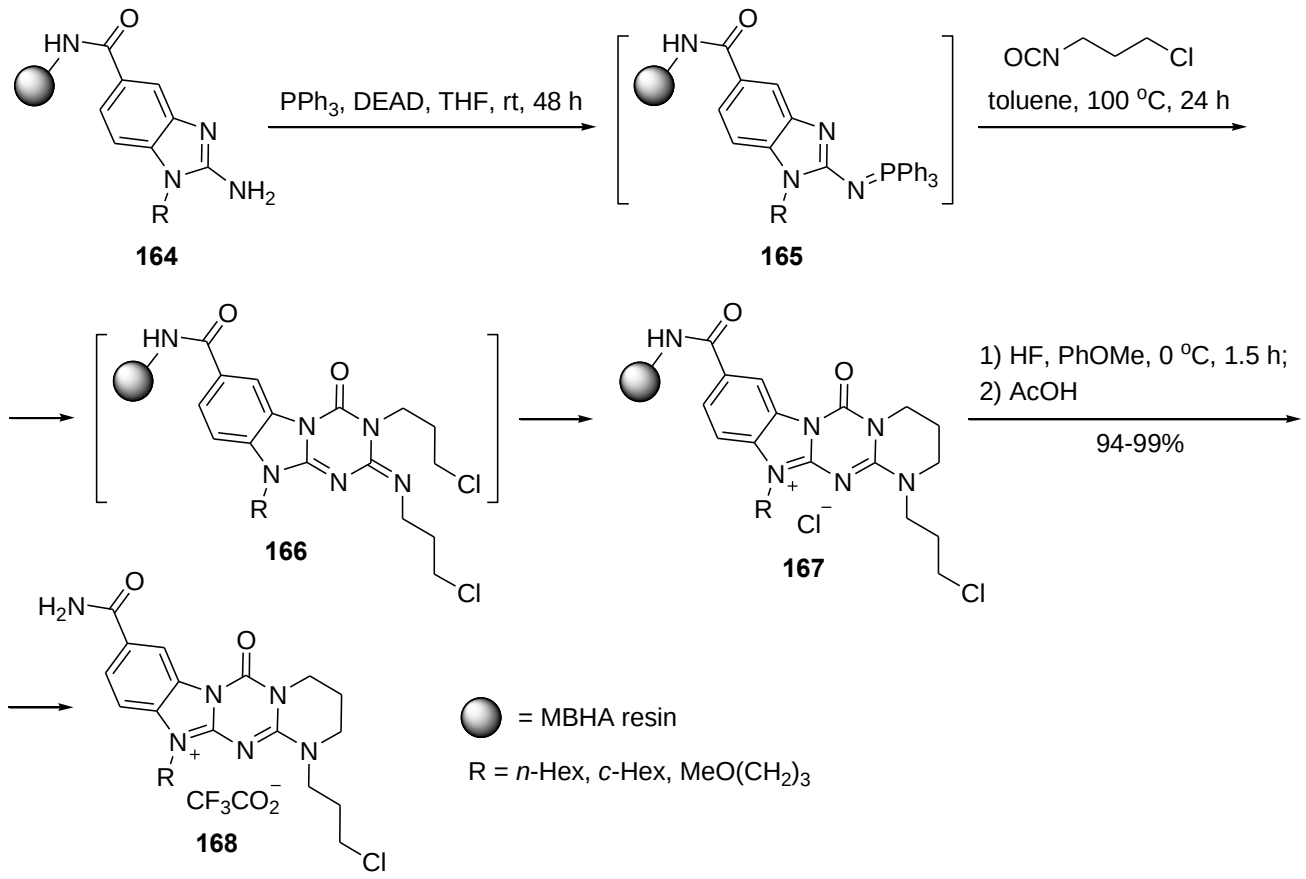
Ceder and Vernmark[70] reported annelation of the pyrimidine and 1,3,5-triazine rings to 2-amino-6-picoline (**161**) using condensation with ethyl *N*-cyanoformimidate (**162**) (Scheme 72). However, 1,3,4-triazacycl[3.3.3]azine (**163**) was isolated in very low yield.



161 **162** **163**

Scheme 72

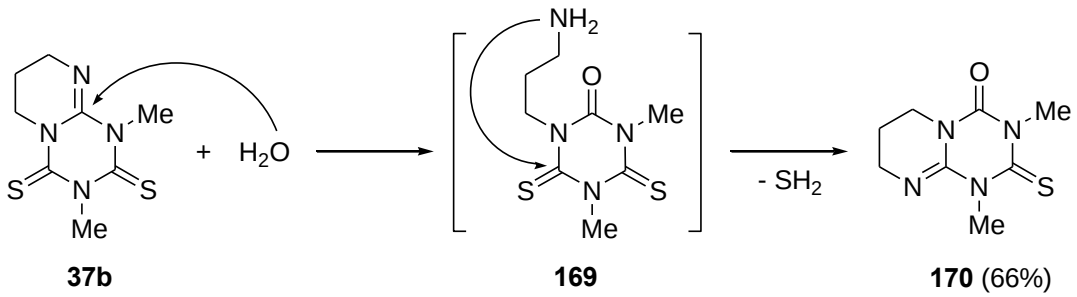
The one-pot solid-phase synthesis of **168** having pyrimido[1,2-*a*][1,3,5]triazine core fused with benzimidazole ring was performed on *p*-methylbenzhydrylamine (MBHA) resin using Houghten's "tea-bag" method[71] (Scheme 73).[72] Resin-bound 2-aminobenzimidazoles **164** were converted to their corresponding iminophosphoranes **165** followed by the treatment with 3-chloropropyl isocyanate. The annelation of 1,3,5-triazine ring occurred *via* the Aza-Wittig reaction concerted with the addition of the second isocyanate molecule to the endocylcic nitrogen atom of benzimidazole ring and the subsequent heterocyclization. The intramolecular nucleophilic substitution of chlorine atom at one of the side chains of **166** resulted in the pyrimidine ring closure affording **167**. After cleavage from the resin, **168** were isolated as major regioisomers with 93-96% regioselectivity of the process and 80-85% purity of the products. The structure assignments were done on the basis of 2D NMR spectroscopy, particularly the HMBC data.



Scheme 73

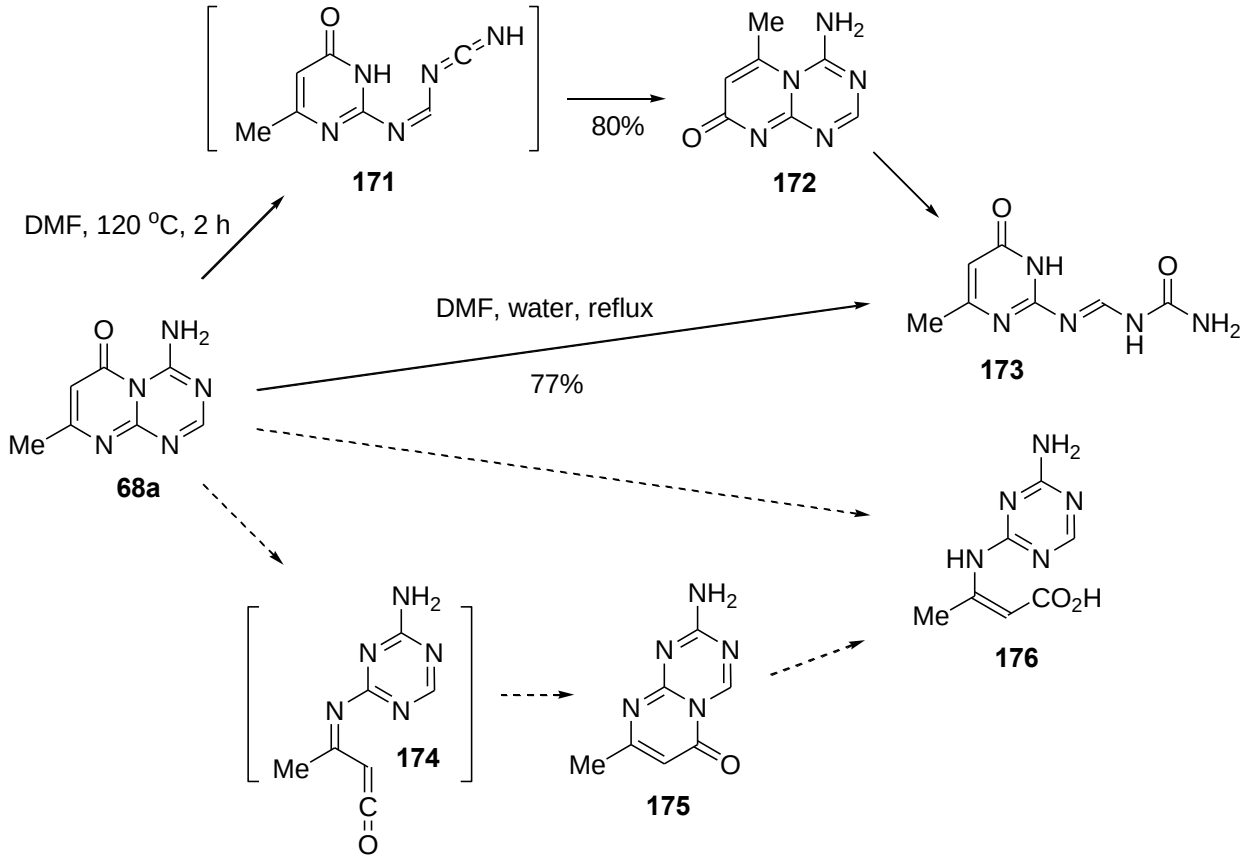
5. REARRANGEMENTS IN PYRIMIDO[1,2-*a*][1,3,5]TRIAZINES WITH RECYCLIZATION OF THE SYSTEM

Two rearrangements of pyrimido[1,2-*a*][1,3,5]triazines leading to pyrimido[1,2-*a*][1,3,5]triazines of different structure were reported.[18,31] In the investigation of the hydrolysis of **37b**, formation of **170** was observed after treatment of **37b** with inorganic base (sodium acetate, sodium carbonate or sodium hydroxide) in water under mild conditions (0 °C) (Scheme 74).[18] It was found that initial step of the reaction involved the hydrolytic pyrimidine ring opening followed by the recyclisation of triazine **169** *via* the intramolecular nucleophilic substitution of thioxo group. The structure of **170** was unambiguously established by X-ray crystallography.[73]



Scheme 74

It was reported[31] that 4-amino-8-methylpyrimido[1,2-*a*][1,3,5]triazin-6-one (**68a**) underwent thermally induced rearrangement to 4-amino-6-methylpyrimido[1,2-*a*][1,3,5]triazin-8-one (**172**) *via* intermediacy of carbodiimide **171**, resulted from the triazine ring opening of **68a** (Scheme 75). Heating **68a** or **172** in aqueous DMF was reported to give formamidine **173** as a result of the hydrolytic 1,3,5-triazine ring opening. However, from the analysis of the provided ^{1}H NMR spectral data, one can suggest an alternative pathway of the rearrangement with the corresponding structure corrections. For example, the ~1.2 ppm downfield shift of the methine proton signal on the triazine ring after the rearrangement should be encountered for the deshielding effect of the neighboring carbonyl group. Therefore, the structure of 2-amino-8-methylpyrimido[1,2-*a*][1,3,5]triazin-6-one (**175**), formed from ketene **174** *via* pyrimidine ring opening of **68a**, can be proposed for the rearranged product (*cf.* Scheme 43). Similarly, hydrolytic cleavage of the pyrimido[1,2-*a*][1,3,5]triazine system of **68a** was likely to proceed *via* the pyrimidine ring opening providing acid **176**, theoretically more stable than formamidine **173**. The spectral data also better correspond to structure **176** rather than **173**. Further investigations are required for complete understanding of this interesting rearrangement.



Scheme 75

6. CONCLUSION

A variety of effective synthetic approaches to the preparation of pyrimido[1,2-*a*][1,3,5]triazines and their polycyclic analogues has been developed. The biological activity of pyrimido[1,2-*a*][1,3,5]triazines has not been systematically studied. However, some reported biological activity data show a good potential for the future exploration in the medicinal and agricultural chemistry of pyrimido[1,2-*a*][1,3,5]triazines. The present review aims to set a background for the research in this area.

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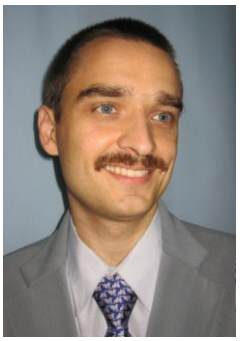

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