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1,2,3-Triazole-4(5)-amines – Convenient Synthetic Blocks for the Construction of Triazolo-Annulated Heterocycles

Abstract

Aim. To analyze and summarize the synthetic potential of 1,2,3-triazole-4(5)-amines as efficient building blocks in the synthesis of triazolo-annulated pyridine, azine and azepine systems.

Results and discussion. Original literature sources revealing the synthetic potential of 4(5)-amino functionalized 1,2,3-triazoles as convenient and available building blocks for the preparation of triazolo-annulated pyridines, azines and azepines were analyzed and systematized. Condensation of 1,2,3-triazole-4(5)-amines with methylene active compounds was shown to be a powerful tool for the synthesis of versatile triazolo[4,5-*b*]pyridines. In turn, the cyclocondensation based on 5-amino-1,2,3-triazole-4-carboxylic acids and their structurally modified derivatives was proven to be a general way for obtaining a number of triazolo[4,5-*d*]pyrimidine systems. Few representatives of triazolo-annulated pyridazines, 1,3-oxazines and 1,3-thiazines were synthesized by the intramolecular cyclization of the corresponding 4-aryl(carboxy-, aminomethyl)-5-amino-1,2,3-triazoles. The cyclocondensation involving 4,5-diamino-, 4-carbofunctionalized 5-amino-1,2,3-triazoles and 4-amino-5-thiocarboxamido-1,2,3-triazoles was successful for the construction of di-, oxa- and thiazepino-annulated triazoles.

Conclusions. The analysis, systematization and summary of the literature regarding the synthetic potential of 1,2,3-triazole-4(5)-amines conclusively demonstrate that these structures are easily available and convenient molecular blocks for the construction of triazolo-annulated pyridine, azine and azepine systems that are important for synthetic and biomedical research.

Keywords: 4(5)-amino-1,2,3-triazoles; triazolo[4,5-*b*]pyridines; triazolo[4,5-*d*]pyridines; triazoloannulated azepines; cyclocondensation

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1,2,3-Триазол-4(5)-аміни – зручні синтетичні блоки для конструювання триазолоанельованих гетероциклів

Анотація

Мета. Проаналізувати та узагальнити синтетичний потенціал 1,2,3-триазол-4(5)-амінів як ефективних білдинг-блоків у синтезі триазолоанельованих піридинових, азинових та азепінових систем.

Результати та їх обговорення. Проаналізовано та систематизовано оригінальні літературні джерела, які розкривають синтетичні можливості 4(5)-амінофункціоналізованих 1,2,3-триазолів як зручних і доступних будівельних блоків для одержання триазолоанельованих азинів та азепінів. Доведено, що конденсація 1,2,3-триазол-4(5)-амінів із метиленактивними сполуками є потужним інструментом синтезу різноманітних триазоло[4,5-*b*]піридинів. Зі свого боку для отримання низки триазоло[4,5-*d*]піримідинових систем досить загальними виявились циклоконденсації на основі 5-аміно-1,2,3-триазол-4-карбонових кислот та їхніх структурно модифікованих похідних. Нечисленних представників триазолоанельованих піридазинів, 1,3-оксазинів та 1,3-тіазинів було синтезовано внутрішньомолекулярними циклізаціями відповідних 4-арил(карбокси-, амінометил)-5-аміно-1,2,3-триазолів. Для конструювання ді-, окса- та тіазепіноанельованих триазолів вдалими виявились циклоконденсації за участю 4,5-діаміно-, 4-карбофункціоналізованих 5-аміно-1,2,3-триазолів та 4-аміно-5-тіокарбоксамідо-1,2,3-триазолів.

Висновки. Аналіз, систематизація та узагальнення літературних джерел, які стосуються синтетичного потенціалу 1,2,3-триазол-4(5)-амінів, переконливо засвідчують, що такого типу структури є доступними й зручними молекулярними блоками для конструювання важливих для синтетичних і біомедичних досліджень триазолоанельованих піридинових, азинових та азепінових систем.

***Ключові слова*:** 4(5)-аміно-1,2,3-триазоли; триазоло[4,5-*b*]піридини; триазоло[4,5-*d*]піримідини; триазолоанельовані азепіни; циклоконденсація

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■ Introduction

1,2,3-Triazole-4(5)-amines, including those additionally modified with other functional substituents and heterocyclic rings, occupy their rightful place in the chemistry of azole compounds and are of great interest to researchers due to their pronounced synthetic capabilities. Particular interest in heterocyclic systems annulated with a triazole ring arose with the discovery of the drug "Ticagrelor" **I** (Figure) indicated to prevent or reduce the risk of coronary thrombosis in patients with the acute coronary syndrome and patients undergoing the percutaneous coronary intervention or coronary artery bypass grafting [1].

Inhibitors of the human carbonic anhydrase isoenzyme type hCA IX **II** [2] and calcium/calmodulin-regulated kinases PIM **III** [3], a potent antagonist of the Dengue virus **IV**, were found in a number of triazoloanelated pyridines [4].

A low molecular weight agonist of cannabinoid receptor 2 (CB2) **V** [5], inhibitors of replication of the Chikungunya virus (CHIKV) **VI** [6] and a reversible inhibitor of lysine-specific demethylase 1 (LSD1) **VII** [7], compounds with the antitumor activity against breast cancer cells MCF-7, lungs A549 **VIII** [8] and lungs H1650 **IX** have been identified among the functionalized triazolo[4,5-*d*]pyrimidines [9].

The bioscreening results of triazolo[4,5-*b*]-[1,5]benzodiazepine **X** showed the antidopaminergic and anticholinergic activity to bind [^{3}H]spiperone and [^{3}H]QNB receptors. The neuroleptic potential of derivatives **X** was evaluated in terms of their ability to induce hypothermia and catalepsy in mice and to block conditioned avoidance reactions in rats [10].

At the same time, despite the wide pharmaceutical profile of heteroannulated 1,2,3-triazole systems, the original works related to the methods of their synthesis based on functionalized 4(5)-aminotriazoles were not subjected to systematic analysis. Thus, it seemed appropriate to comprehensively summarize the published literature on the use of 1,2,3-triazole-4(5)-amines for the preparation of triazoloannulated six- and seven-member heterocyclic systems.

■ Results and discussion

1. The synthesis of triazolo[4,5-*b*]pyridines

5-Aminotriazoles **1** as heterocyclic analogs of enamines were successfully used in the three-component condensation with 5-chloroisatin (**2**) and Meldrum's acid (**3**) to obtain a series of spirotriazolopyridones **4** and **5** (Scheme 1) [4, 11, 12]. Thus, using (*S*)- and (*R*)-1-[1-(4-chlorophenyl)ethyl]-1*H*-1,2,3-triazole-5-amines **1**, diastereomeric mixtures of optically pure spiro-derivatives **4** and **5** were synthesized. Instead, the condensation of 1-(4-chlorobenzyl)- and 1-[(5-chloropyridin-2-yl)-methyl]-1*H*-1,2,3-triazole-5-amines **1** led to the formation of a mixture of enantiomers, of which the preparative high-performance liquid chiral chromatography yielded only (*R*)-diastereomer **4**. In the case of 1-[1-(4-chlorophenyl)ethyl(propyl)]-1*H*-1,2,3-triazole-5-amines **1**, racemate reaction products were isolated.

4-Functionalized 5-amino-1,2,3-triazoles also proved to be convenient building blocks for the synthesis of substituted triazolo[4,5-*b*]pyridine derivatives. Thus, the treatment of 5-amino-4-formyltriazoles **6** with an excess of acetone or ethyl acetoacetate **7** in an aqueous solution of NaOH or

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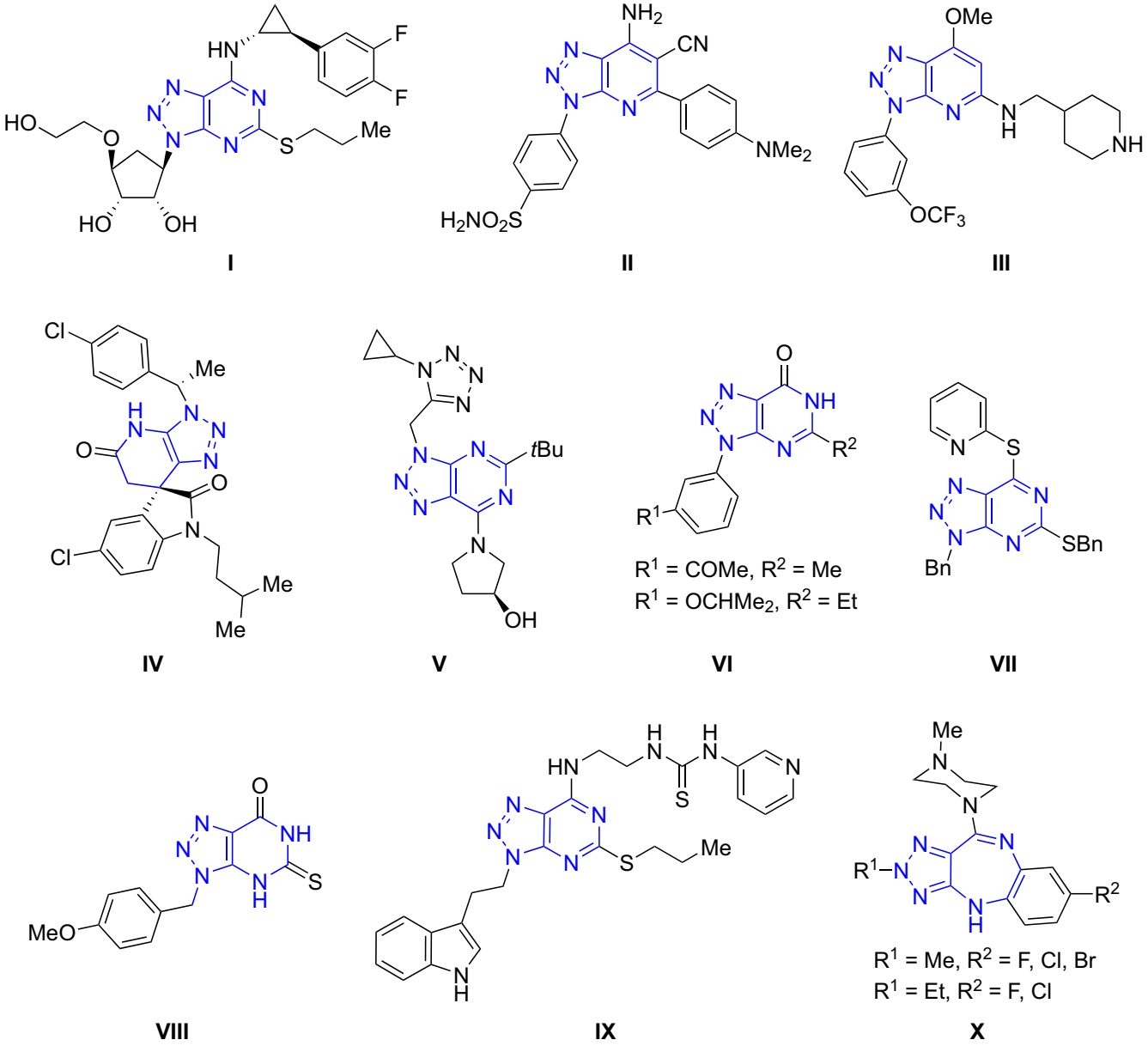
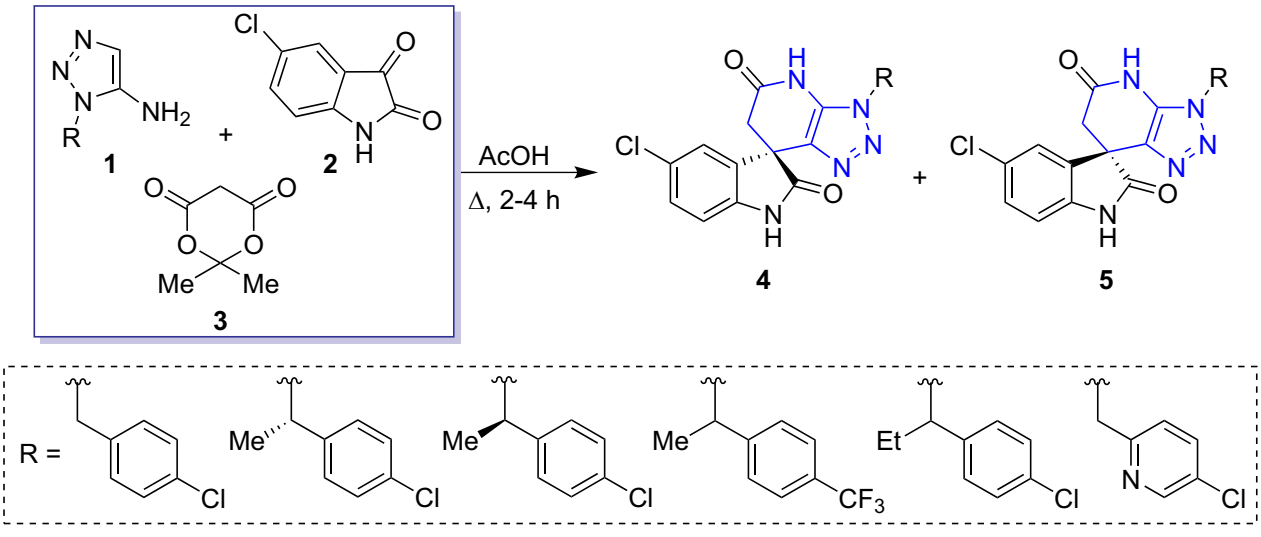
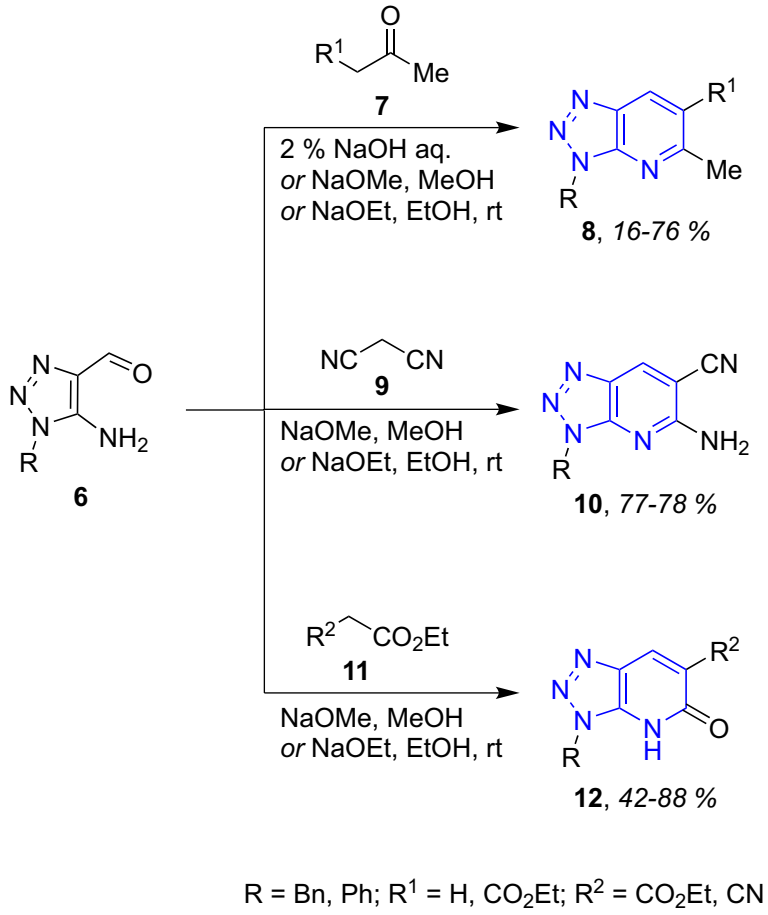


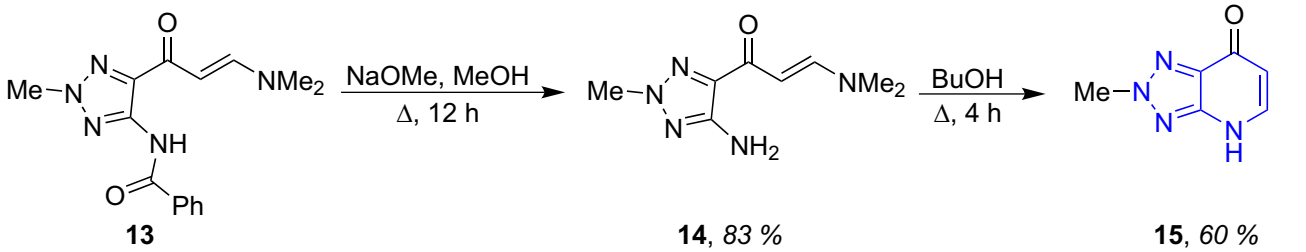
Figure. The structures of the drug «Ticagrelor» **I** and bioactive triazoloannulated heterocycles **II-X**



Scheme 1. The synthesis of spirotriazolopyridones **4, 5**



Scheme 2. The cyclocondensation of 5-amino-4-formyltriazoles **6** with active methylene compounds



Scheme 3. The synthesis of 2-methyltriazolo[4,5-*b*]pyridin-7-one **15**

in an alcoholic solution of sodium alkoxide yielded di- and trisubstituted 1,2,3-triazolo[4,5-*b*]pyridine **8** (Scheme 2) [13]. In turn, their cyclocondensation with malononitrile (**9**) led to the formation of 5-amino-1,2,3-triazolo[4,5-*b*]pyridine-6-carbonitriles **10**, and with ethyl malonate or ethyl cyanoacetate **11** produced 3,6-disubstituted 1,2,3-triazolo[4,5-*b*]pyridine-5(4*H*)-ones **12**.

The cyclization of 5-amino-4-[3-(dimethylamino)acryloyl]-2-methyl-1,2,3-triazole (**14**) obtained from the corresponding *N*-{5-[3-(dimethylamino)-acryloyl]-2-methyl-2*H*-1,2,3-triazol-4-yl}benzamide (**13**) proved to be effective for the preparation of 2-methyltriazolo[4,5-*b*]pyridin-7-one (**15**) (Scheme 3) [14].

The interaction of 4-acetyltriazole-2-phenyl-5-amine (16) with malononitrile (**9**) in boiling DMF led to the formation of 5-aminotriazolo[4,5-*b*]pyridine-6-carbonitrile (**17**), while the acetylation with acetic anhydride yielded derivative **18** condensed with dimethylformamide dimethylacetal (DMFDMA) to give *cis*-enaminone **19** (Scheme 4). The latter underwent the cyclization upon the treatment with phenyldiazonium chloride (**20**) under basic conditions, followed by the deacylation, and formed [1,2,3]triazolo[4,5-*b*]pyridin-7-one (**21**) [15].

The authors of [16] have developed an easy variant of the synthesis of triazolo[4,5-*b*]pyridin-5-ones **24**, which includes the interaction of 4-acyltriazole-5-amines **16** with carboxylic acids or esters **22** under the microwave irradiation with the formation of the corresponding acetamides **23**; the cyclization of the latter in boiling DMF yields target products **24** (Scheme 5).

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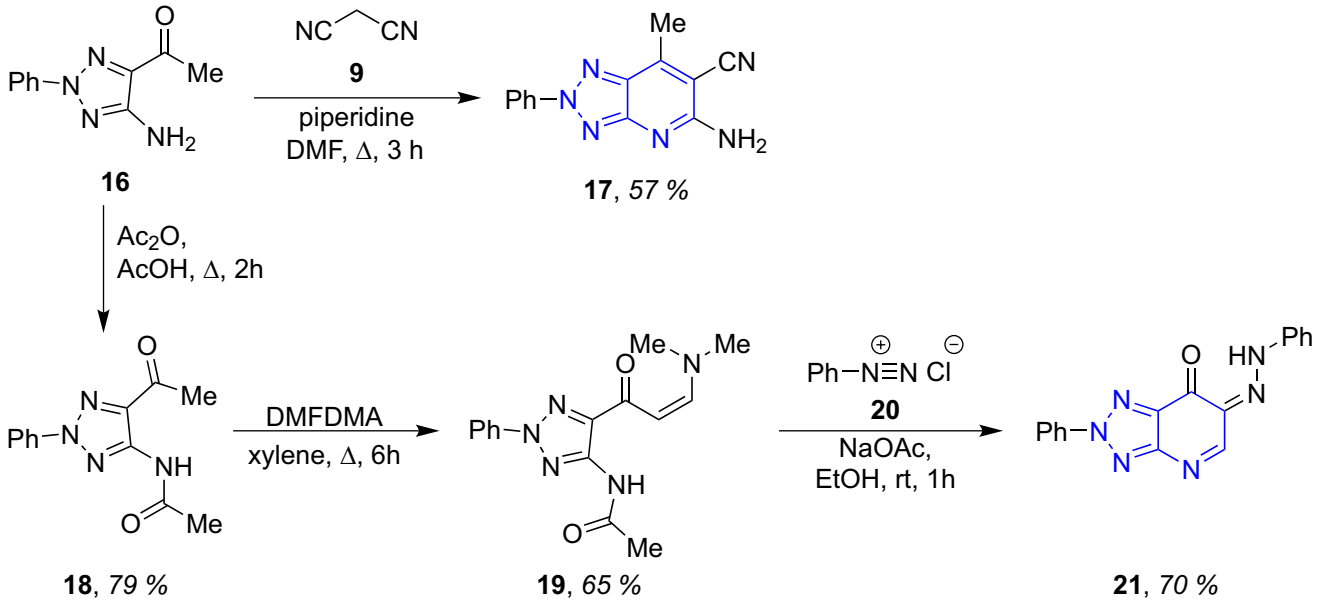
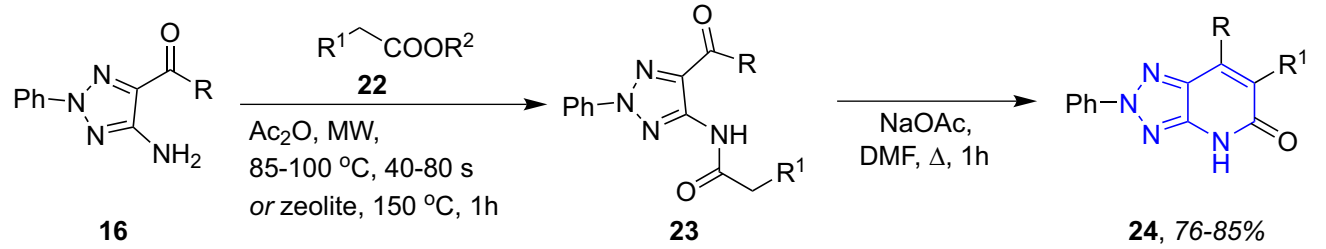


Scheme 4. Synthetic possibilities of 4-acetyltriazole-5-amine **16**



R = Me, Ph
R^1 = CN, CO_2Et, MeCO, PhCO, 4-NO_2-C_6H_4
R^2 = H, Et

Scheme 5. The method for the synthesis of trisubstituted triazolo[4,5-*b*]pyridin-5-ones **24**

The condensation of 5-aminotriazole-4-carbonitrile **25** with ethyl cyanoacetate (**11**) led to 7-amino-5-oxotriazolo[4,5-*b*]pyridine-6-carbonitrile **26**, and with benzylidene derivatives **27** to 7-aminotriazolo[4,5-*b*]pyridine-6-carbonitriles **28** (Scheme 6) [2].

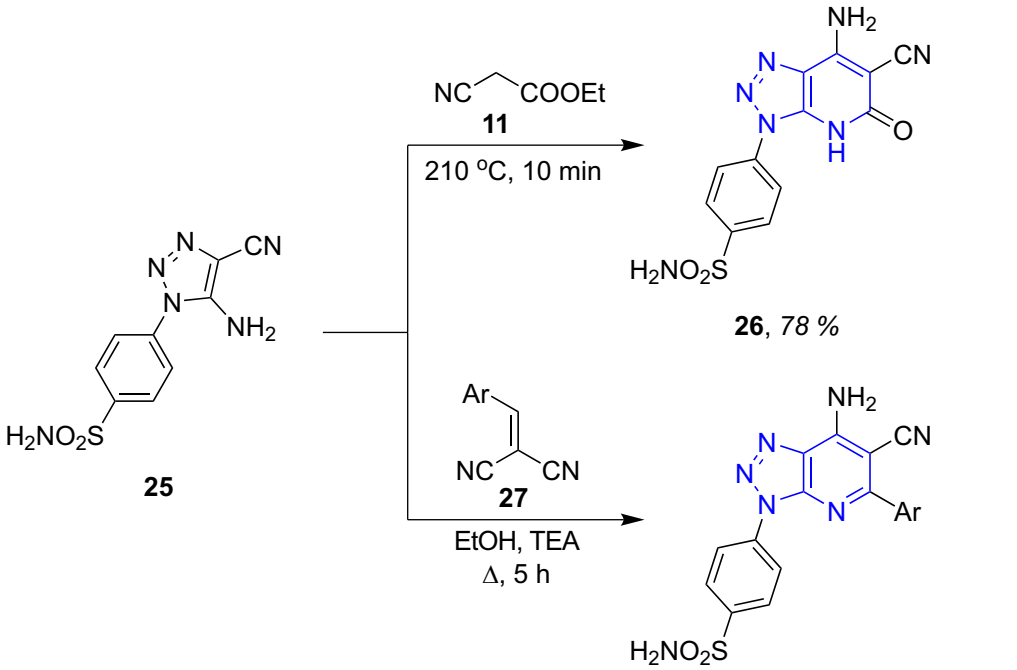
A convenient method for the synthesis of 7-aminotriazolo[4,5-*b*]pyridine-6-carboxylates **31** is based on the reaction of aminonitriles **29** with acetoacetic ester (**30**) in the presence of a Lewis acid (Scheme 7) [17].

The reaction of triazolylaminonitrile **32** with nickel complexes of 1,3-dicarbonyl compounds **33** proved to be successful in the preparation of triazoloannulated pyridines **34** (Scheme 8) [18].

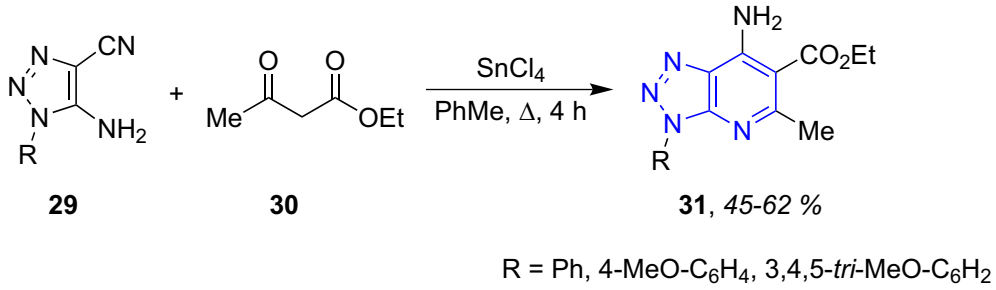
The authors [19] proposed effective conditions for the Friedlaender reaction of *N*-Boc-4-aminotriazole-5-carbaldehydes **35** with acetylacetone (**36**) or malononitrile (**9**) which resulted in the formation of target 6-acetyltriazolo[4,5-*b*]pyridines **37** and 5-aminotriazolo[4,5-*b*]pyridine-6-carbonitriles **38**, respectively (Scheme 9).

It was found that heating of *N*-Boc-4-aminotriazole-5-carbaldehydes **35** with malonic acid (**39**) in acetic acid at 100°C in the presence of catalytic amounts of pyrrolidine led to the formation of 5-oxo-4,5-dihydro-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine-6-carboxylic acids **40** previously undescribed in 61–66% yields (*Method A*) (Scheme 10). However, the use of Meldrum's acid (**3**), a synthetic equivalent of malonic acid, in this process under similar reaction conditions is much more productive since it increases the yield of the target compounds to 91–94% (*Method B*). The likely transformation scheme in the case of malonic acid is through intermediate products **A** and **B**, while in the case of Meldrum's acid it is through **C** and **D**. Indeed, the efficiency of the latter is due to the structure of intermediate **D** which, in contrast to intermediate **B**, is characterized by much higher selectivity of further transformation [20].

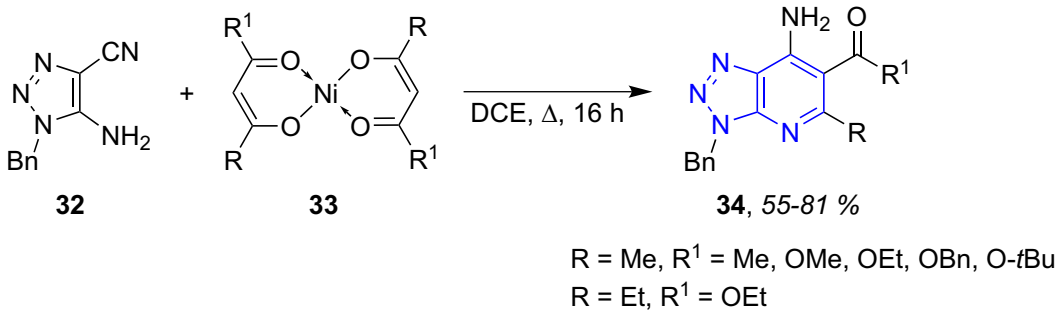
To obtain new heterocyclic analogs of carboannulated triazolopyridines as promising bioactive



Scheme 6. The synthesis of 7-aminotriazolo[4,5-*b*]pyridine-6-carbonitriles **26** and **28**



Scheme 7. The synthesis of 7-aminotriazolo[4,5-*b*]pyridine-6-carboxylates **31**



Scheme 8. The reaction of 5-aminotriazole-4-carbonitrile **32** with nickel complexes

compounds, aminoaldehydes **35** were tested in the cyclocondensation with cycloalkanones **41** and 1,3-cyclohexanediones **43**, which made it possible to isolate carbocyclic derivatives **42** and hydrogenated 1,2,3-triazolo[4,5-*b*]quinolines **44**, respectively (Scheme 11) [19].

Another method for the formation of the triazolo[4,5-*b*]quinoline core reported by the authors of the patent [21] was the use of the intramolecular cyclization of 4-*N*-arylamino-substituted 1,2,3-triazole-5-carboxylic acids **45** by their heating in polyphosphoric acid (Scheme 12).

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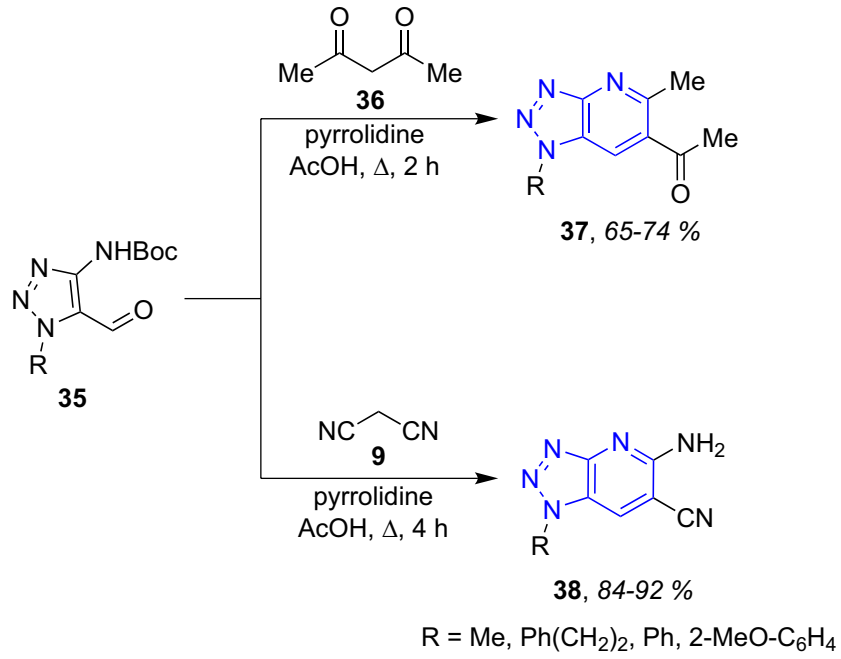
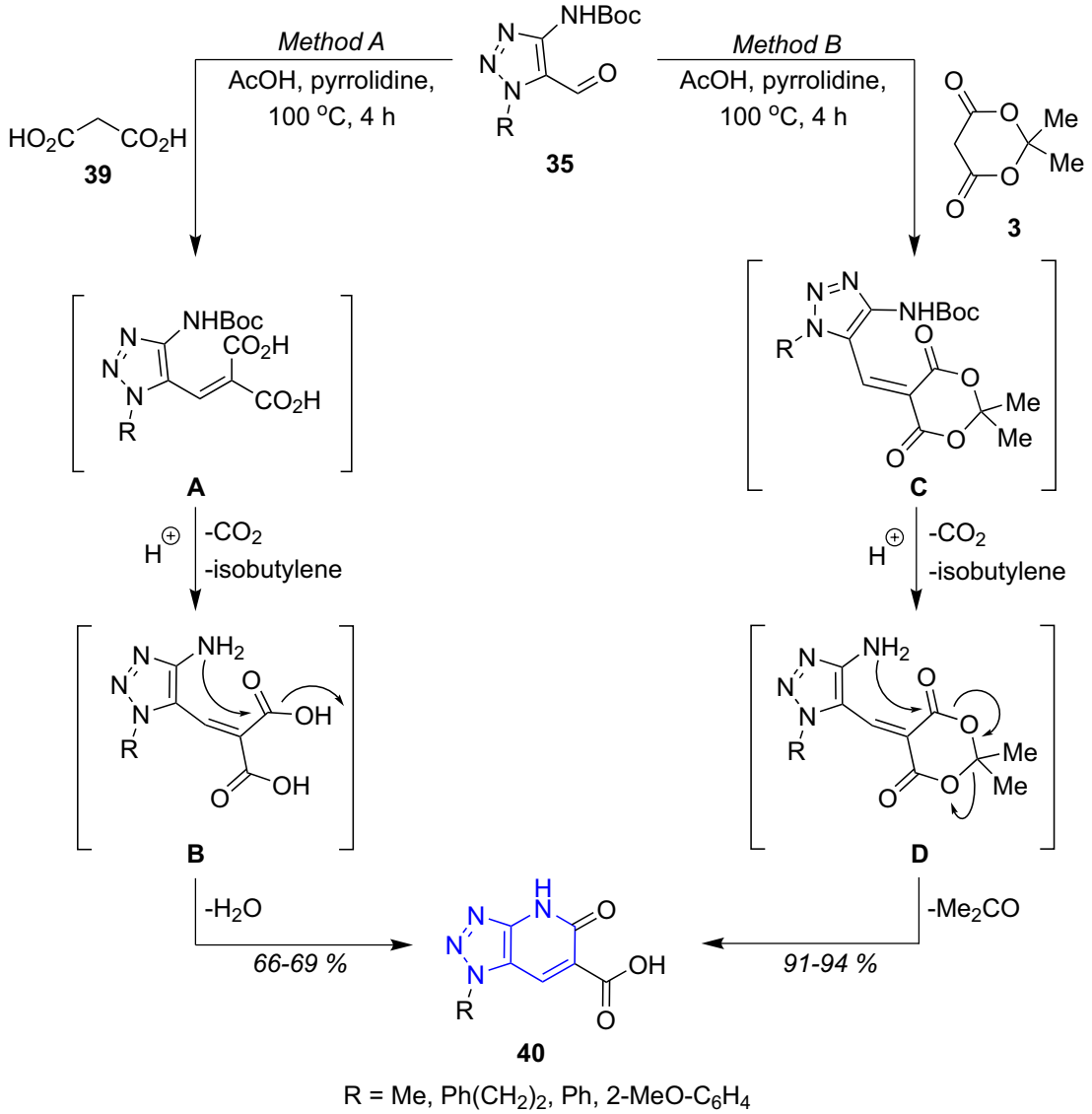
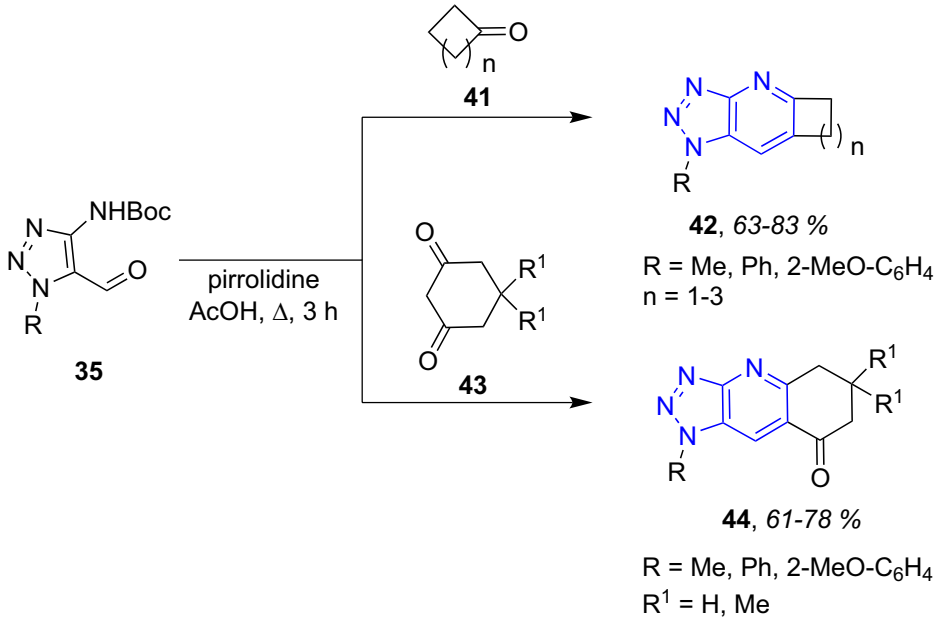


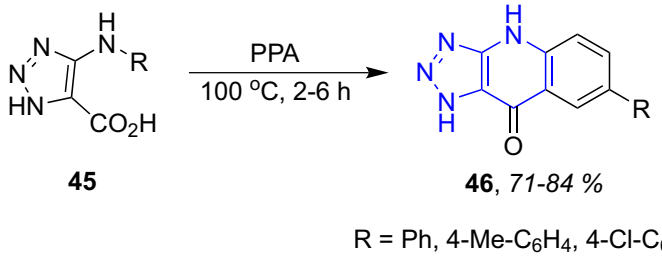
Scheme 9. The reaction of *N*-Boc-4-aminotriazole-5-carbaldehydes **35** with active methylene compounds



Scheme 10. The synthesis of 5-oxo-4,5-dihydro-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine-6-carboxylic acids **40**



Scheme 11. The synthesis of carbocyclic triazolopyridines **42** and **44**



Scheme 12. The intramolecular cyclization of 4-*N*-arylamino-substituted 1,2,3-triazole-5-carboxylic acids **45**

2. The synthesis of triazolo[4,5-*d*]pyrimidines

2.1. Reactions involving 5-amino-1,2,3-triazole-4-carboxylates

An important field of application of aminofunctionalized 1,2,3-triazoles has become the development of a method for the synthesis of triazolo[4,5-*d*]pyrimidines, which can be considered as isosteres of biologically promising purines.

Thus, the reaction of carboxylates **47** with triethyl orthoformate gave the corresponding 5-ethoxymethyleneamino-1,2,3-triazoles **48**, which were easily cyclized to 6-aminotriazolo[4,5-*d*]pyrimidin-7-ones **49** by the action of hydrazine hydrate (Scheme 13) [22]. Instead, the reaction of triazoles **47** in the hydrazine solution after 3 h of boiling led to 5-amino-1,2,3-triazole-4-carbohydrazides **50**, which heterocyclization with triethyl orthoformate proved to be effective for obtaining (triazolo[4,5-*d*]pyrimidine-6-yl)formimidates **51**. In turn, the treatment of triazoles **47** with an excess of primary amine **52** in the presence of NH_4Cl at 200°C led to aminoamides **53**, which upon prolonged heating with triethyl orthoformate yielded the target triazolo[4,5-*d*]pyrimidines **54**.

The reaction of aminoester **55** with imidoyl chloride **56** catalyzed by a Lewis acid under the microwave irradiation resulted in the synthesis of triaryl-substituted triazolo[4,5-*d*]pyrimidinone **57** (Scheme 14) [23, 24].

The high-temperature cyclocondensation of 1-hetaryl-substituted 5-amino-1,2,3-triazole-4-carboxylate **58** with urea or thiourea resulted in the formation of triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione and its 5-thio analog **59**, respectively (Scheme 15) [25].

The authors [26] developed a two-stage method for the synthesis of *bis*[1,2,3]triazolo[1,5-*a*:4',5'-*e*]pyrimidinones **62**, the first stage of it was azidation of amines **60** to the corresponding 5-azido-1,2,3-triazolocarboxylates **61**, and the second stage was their cyclocondensation with active methylene nitriles **9** leading to the target products (Scheme 16).

A number of works [27–33] describe an approach that is widely used to activate the triazole amino group with reduced nucleophilicity. For this purpose, 5-amino-1-aryl-1,2,3-triazole-4-carboxylates **63** were converted by the action of Ph_3P into the corresponding iminophosphoranes **64**.

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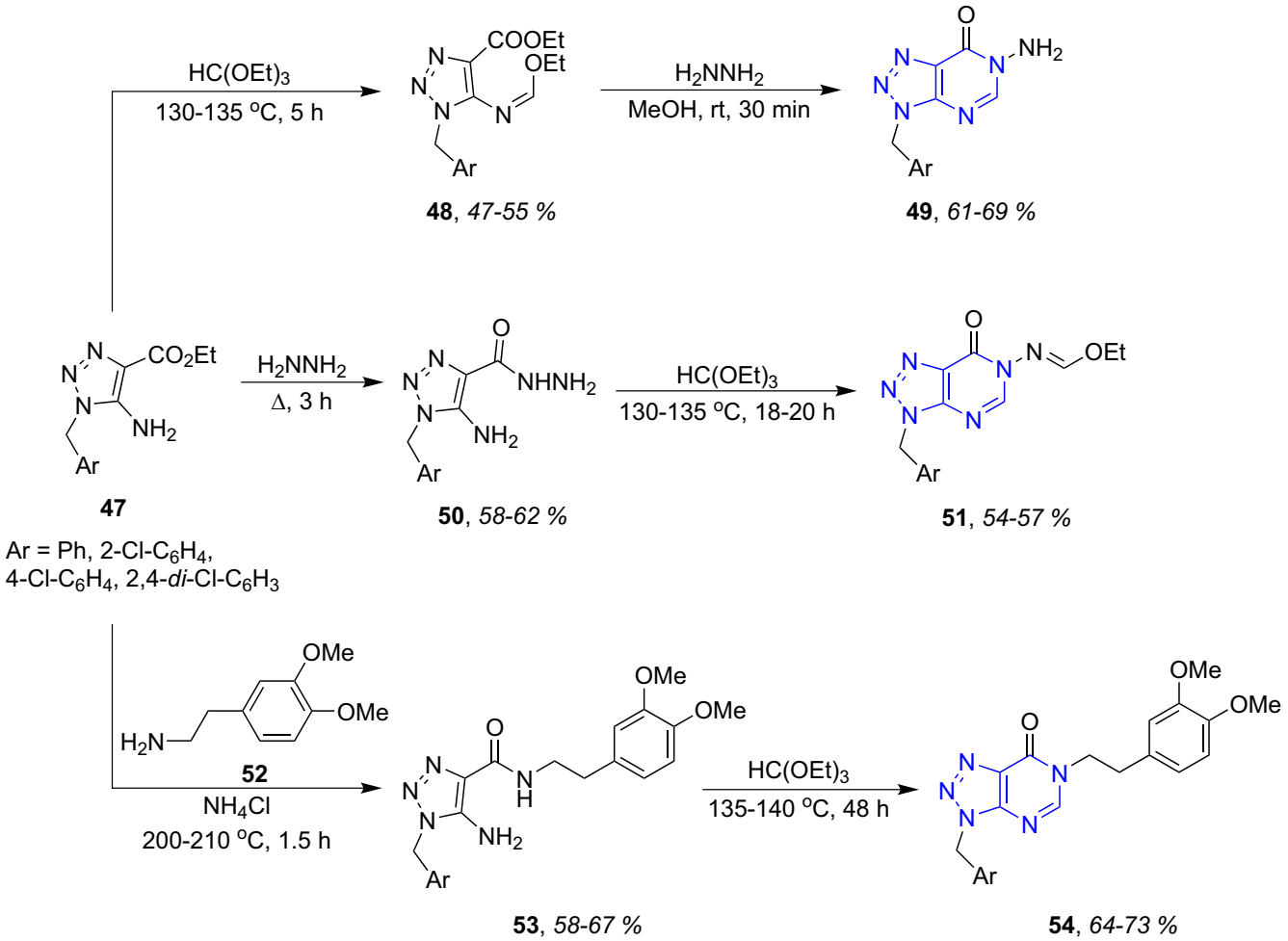
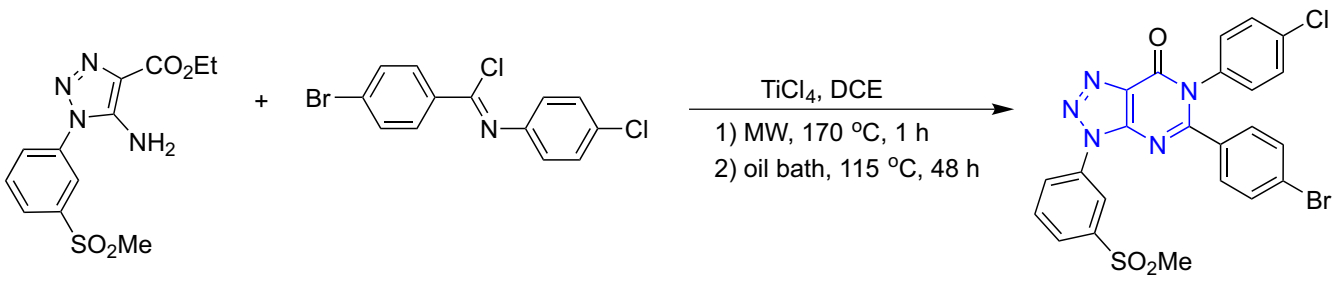
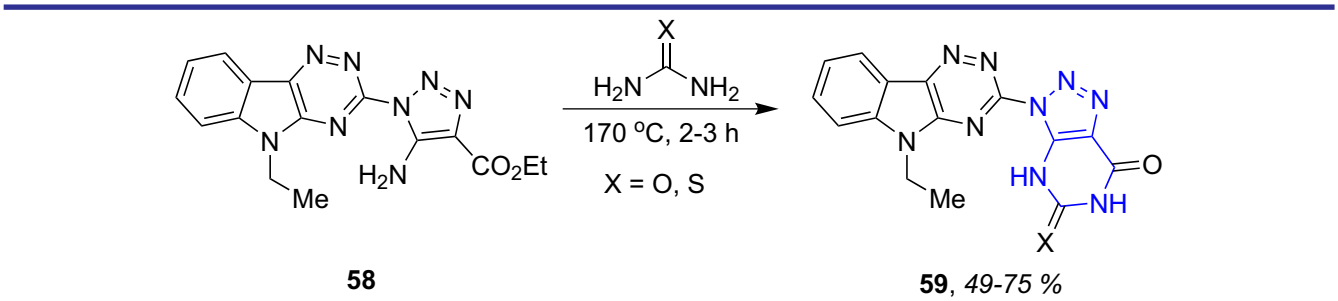


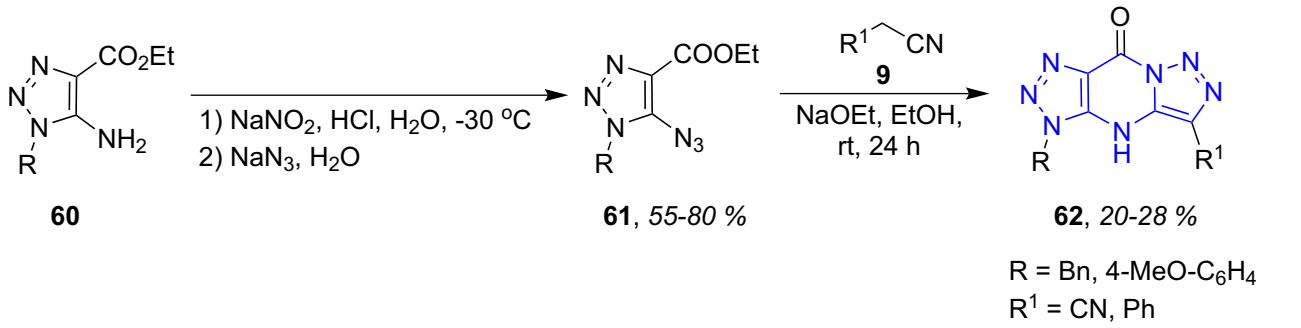
Scheme 13. Preparation of 6-functionalized triazolo[4,5-*d*]pyrimidin-7-ones **49**, **51**, **54**



Scheme 14. The microwave synthesis of triazolo[4,5-*d*]pyrimidin-7-one **57**



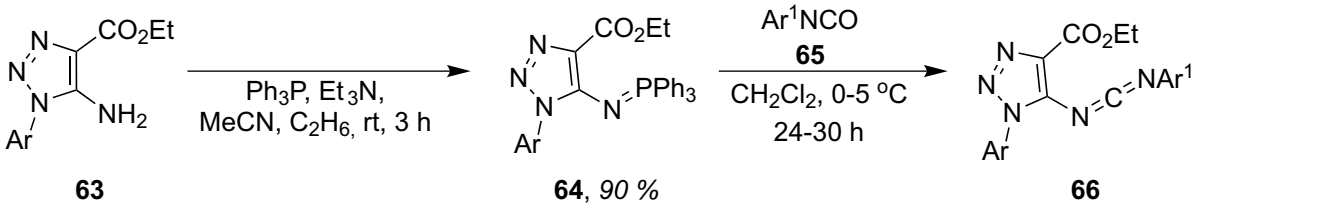
Scheme 15. The cyclocondensation of aminoester **58** with (thio)urea



60 **61**, *55-80 %* **62**, *20-28 %*

R = Bn, 4-MeO-C_6H_4
R^1 = CN, Ph

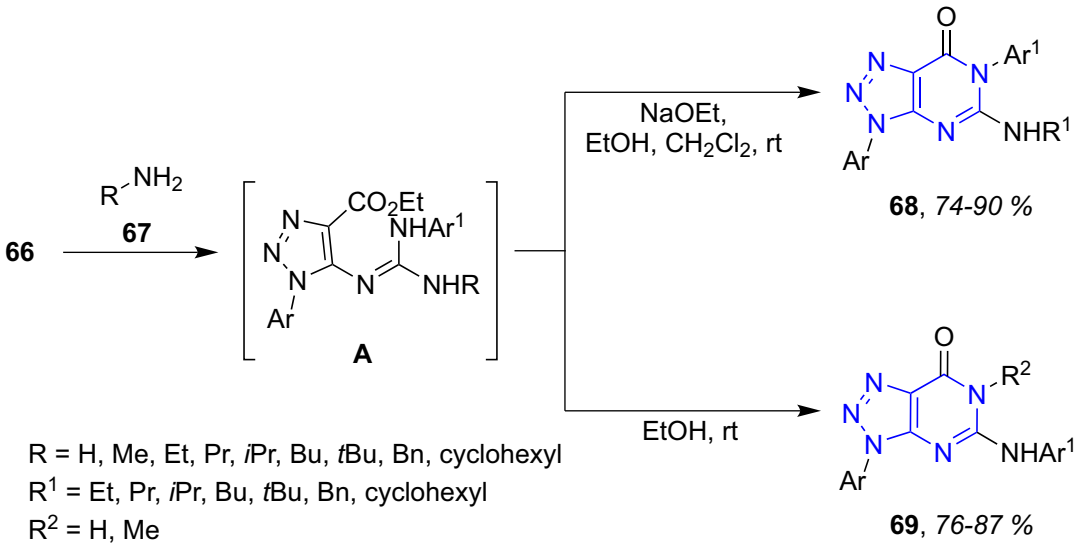
Scheme 16. The synthesis of *bis*[1,2,3]triazolo[1,5-*a*:4',5'-*e*]pyrimidinone **62**



63 **64**, *90 %* **66**

Ar = Ph, 4-Cl-C_6H_4
Ar^1 = Ph, 3-Cl-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4

Scheme 17. The synthesis of triazolyl-containing carbodiimides **66**



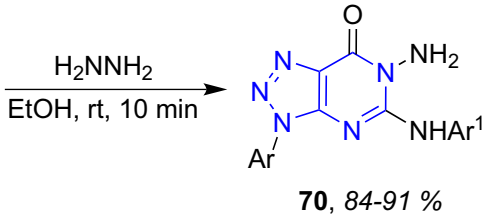
R = H, Me, Et, Pr, *i*Pr, Bu, *t*Bu, Bn, cyclohexyl
R^1 = Et, Pr, *i*Pr, Bu, *t*Bu, Bn, cyclohexyl
R^2 = H, Me

Scheme 18. Preparation of isomeric 5-alkylamino- and 5-arylaminotriazolo[4,5-*d*]pyrimidin-7-ones **68** and **69**

The latter easily underwent *aza*-Wittig reaction with aromatic isocyanates **65** to form triazolyl-containing carbodiimides **66** which had found wide application as effective precursors for the synthesis of triazolo[4,5-*d*]pyrimidines (Scheme 17).

The authors of [27] showed that the interaction of carbodiimides **66** with a number of alkylamines **67** in the presence of NaOEt led to the selective formation of 5-alkylaminotriazolo[4,5-*d*]pyrimidin-7-ones **68** (Scheme 18). At the same time, the formation of regioisomeric 5-arylaminoderivatives **69** was observed under the action of ammonia or methylamine in the absence of a base.

The reaction of triazolylcarbodiimides **66** with hydrazine hydrate in alcohol at room temperature also led to 5-arylamino-6-aminotriazolo[4,5-*d*]pyrimidin-7-ones **70** (Scheme 19) [29].



70, *84-91 %*

Scheme 19. The synthesis of 5-arylamino-6-aminotriazolo[4,5-*d*]pyrimidin-7-ones **70**

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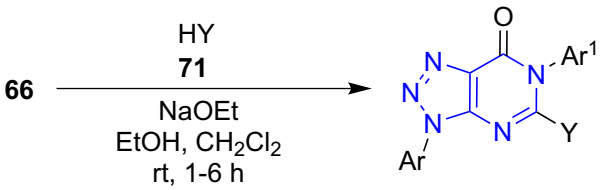


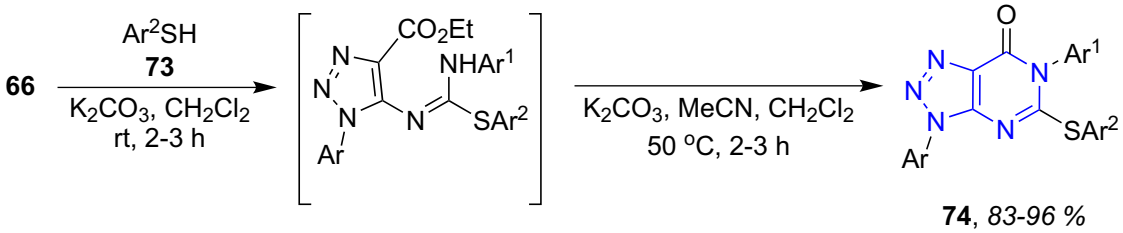
72, *55-92 %*

Y = NEt_2, NPr_2, NBu_2, $N(nC_5H_{11})_2$, $N(nC_6H_{13})_2$, $N(CH_2)_5$, $N(CH_2)_4O$, $N(iBu)_2$, NMe(Ph), $N(iPr)_2$, OMe, OEt, OPr, OBu, O-*i*Pr, OCH_2CCH, $OCH_2CH{=}CH_2$, OPh, 4-Me-C_6H_4O, 4-MeO-C_6H_4O, 4-Cl-C_6H_4O

Ar = Ph, 4-Cl-C_6H_4

Ar^1 = Ph, 4-Cl-C_6H_4, 3-Me-C_6H_4

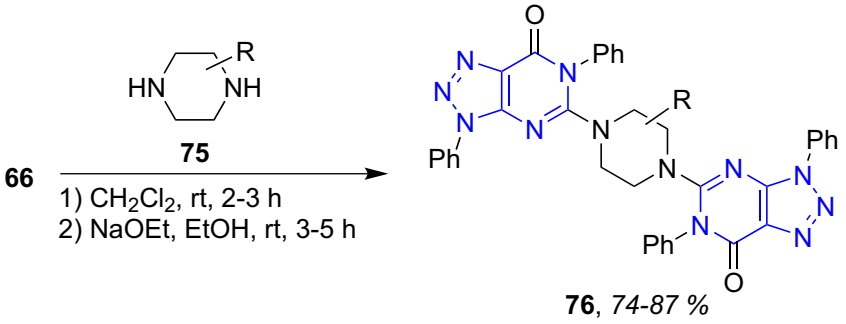
Scheme 20. The synthesis of 5-substituted triazolo[4,5-*d*]pyrimidin-7-ones **72**



74, *83-96 %*

Ar^2 = Ph, 2-Cl-C_6H_4, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4

Scheme 21. The synthesis of 5-arylthiotriazolo[4,5-*d*]pyrimidin-7-ones **74**



76, *74-87 %*

R = H, 2-Me, 2,5-*di*-Me, 2,6-*di*-Me, 2-Et

Scheme 22. The synthesis of 1,4-*bis*[triazolo[4,5-*d*]pyrimidin-7(6*H*)-one]piperazines **76**

To expand the boundaries of the reaction and synthesize various 5-substituted triazolo[4,5-*d*]-pyrimidin-7-ones **72**, *N,N*-dialkylamines, secondary amines and phenols **71** were used as nucleophilic reagents for the formation of a pyrimidine ring based on carbodiimides **66** (Scheme 20) [28, 30].

The reaction of carbodiimides **66** with thiophenols **73** at room temperature did not give the expected cyclization products, whereas at 50°C it yielded 5-arylthiotriazolo[4,5-*d*]pyrimidin-7-ones **74** [32, 33], among which compounds with high herbicidal activity against rapeseed and common flatweed were found (Scheme 21).

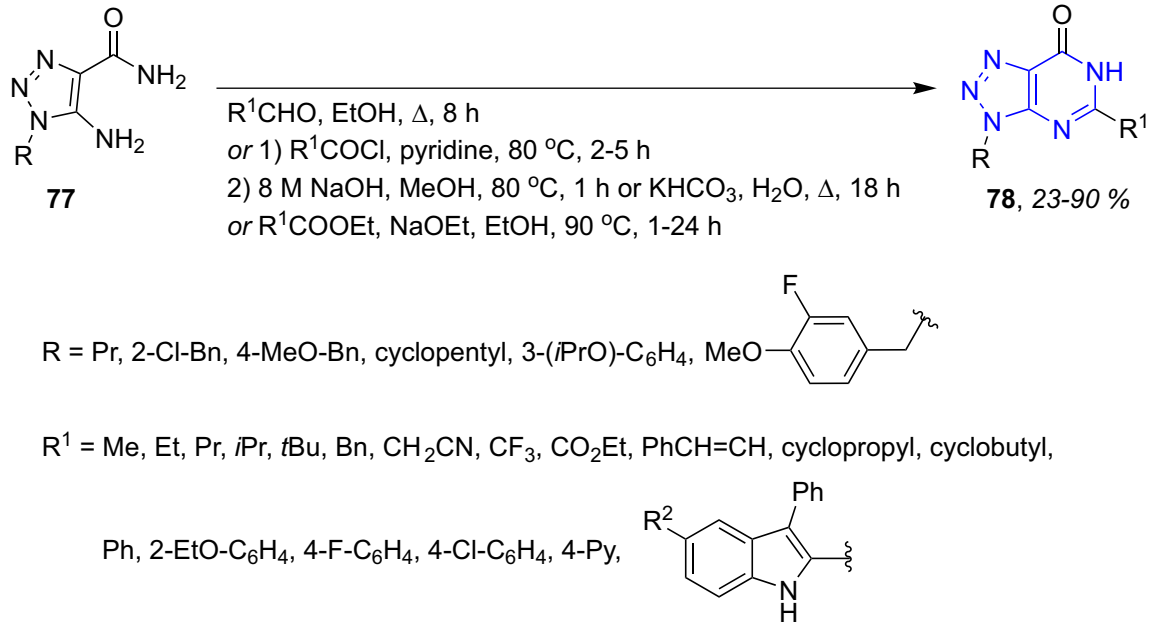
1,4-*Bis*[triazolo[4,5-*d*]pyrimidin-7(6*H*)-one]-piperazines **76** were readily prepared by reacting carbodiimides **66** with substituted piperazines **75** (Scheme 22) [31].

2.2. The cyclization of 5-amino-1,2,3-triazole-4-carboxamides

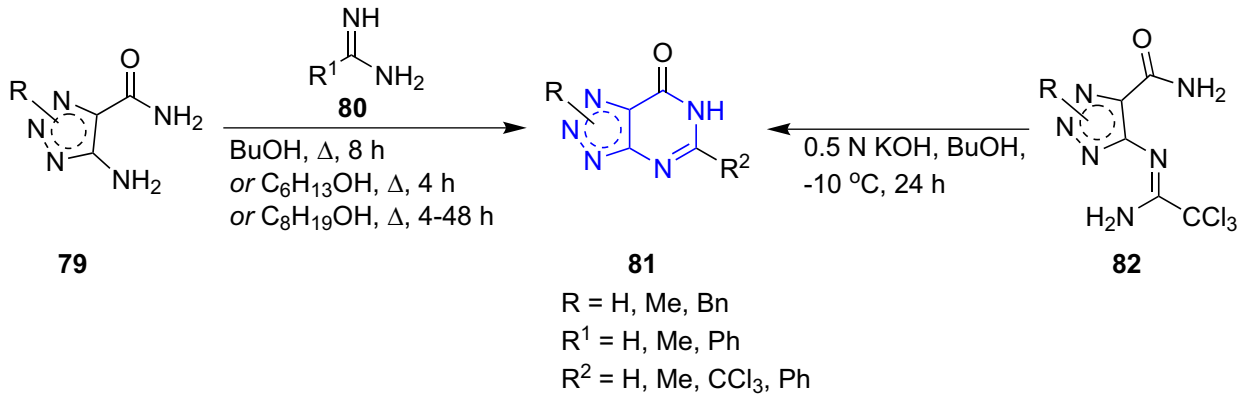
An effective approach to the synthesis of 3,5-disubstituted 1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones **78** is the cyclocondensation of 5-amino-triazole-4-carboxamides **77** with benzaldehydes [8, 34], acyl chlorides [5, 35–39] and esters of mono- and dicarboxylic acids [6, 40–45] (Scheme 23).

The authors of [46] used the cyclocondensation of triazoloaminoamides **79** with amidines **80** to synthesize triazolo[4,5-*d*]pyrimidinones **81**, as well as the intramolecular cyclization of [(1-amino-2,2,2-trichloroethylidene)amino]triazolocarboxamides **82** under basic conditions (Scheme 24).

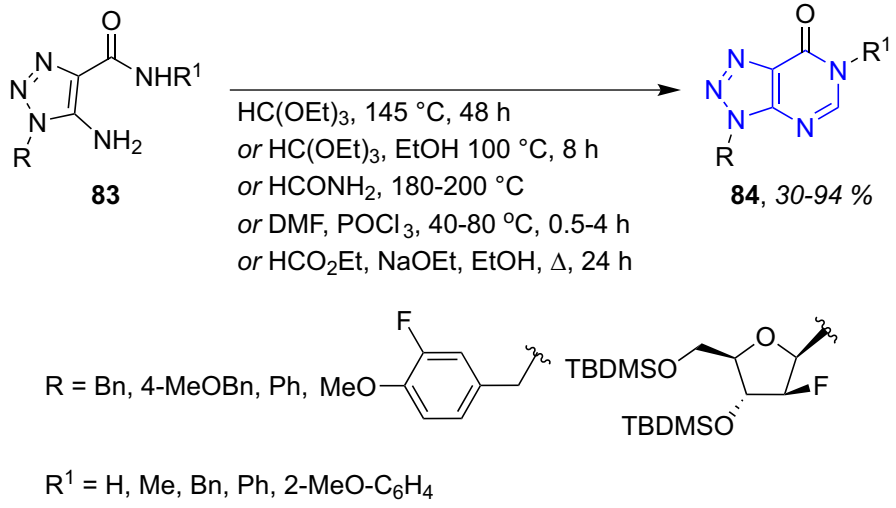
To build a pyrimidine ring based on 5-amino-4-triazolocarboxylic acid amides **83** and to form 3,6-disubstituted triazolo[4,5-*d*]pyrimidin-7-ones **84**



Scheme 23. 5-Aminotriazole-4-carboxamides **77** in the synthesis of triazolo[4,5-*d*]pyrimidin-7-ones



Scheme 24. Approaches to the construction of a triazolo[4,5-*d*]pyrimidine core based on triazoloaminoamides



Scheme 25. The synthesis of 3,6-disubstituted triazolo[4,5-*d*]pyrimidin-7-ones **84**

orthoesters [8, 34, 47, 48], amides and formic acid esters were used as one-carbon reagents [41, 49–51], as well as Vilsmeier-Haack reagent [50] (Scheme 25).

A similar scheme of a high-temperature condensation of 4-aminotriazole-5-carboxamide **85** with formamide was used to obtain 1-methyltriazolo[4,5-*d*]pyrimidin-7-one (**86**) (Scheme 26) [52].

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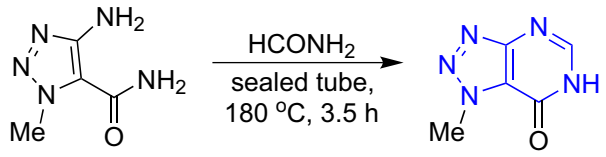
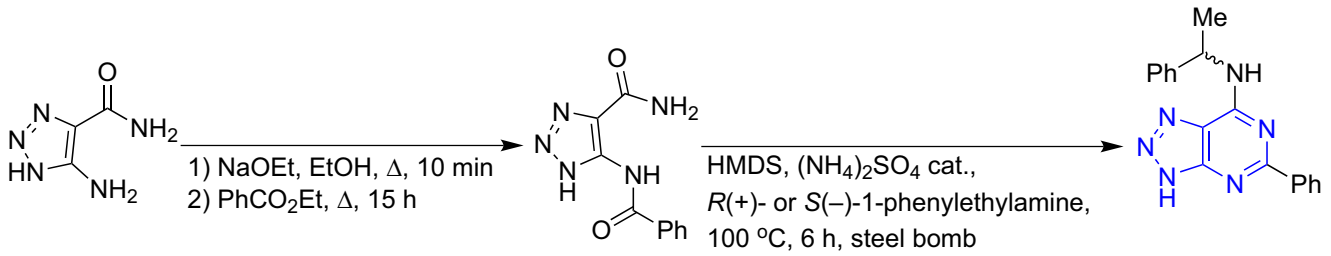


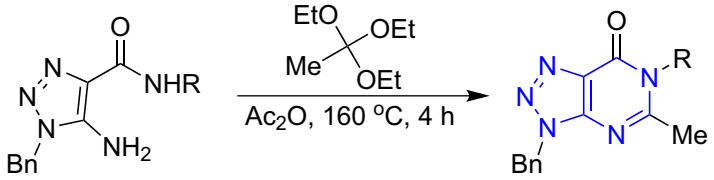
85 **86**, *66 %*

Scheme 26. The synthesis of 1-methyltriazolo[4,5-*d*]pyrimidin-7-one **86**



87 **88**, *65 %* **R-89**, *7.7 %* **S-89**, *5.4 %*

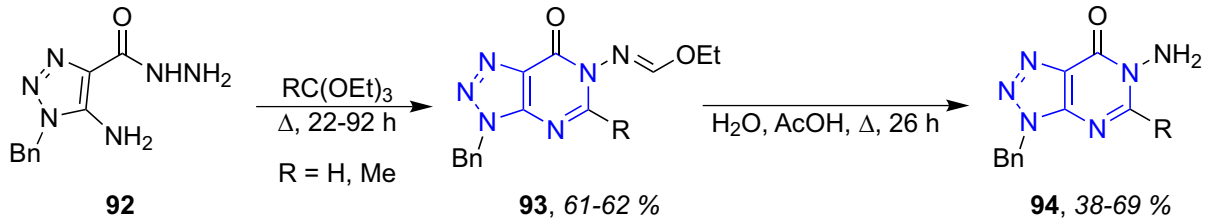
Scheme 27. The synthesis of triazolo[4,5-*d*]pyrimidines **89**



90 **91**, *40-90 %*

R = H, Me, Bn, Ph

Scheme 28. The synthesis of 6-alkyl(aryl)substituted triazolo[4,5-*d*]pyrimidines **91**



92 **93**, *61-62 %* **94**, *38-69 %*

Scheme 29. Preparation of 6-aminotriazolo[4,5-*d*]pyrimidine **94**

5-Benzamidotriazole-4-carboxamide (**88**) obtained from 5-amino-4-carbamoyl-1,2,3-triazole (**87**) by the action of hexamethyldisilazane (HMDS), catalytic amounts of $(NH_4)_2SO_4$ and *R*- or *S*-1-phenylethylamine was converted into 6-aminotriazolo[4,5-*d*]pyrimidines **89** (Scheme 27) [53].

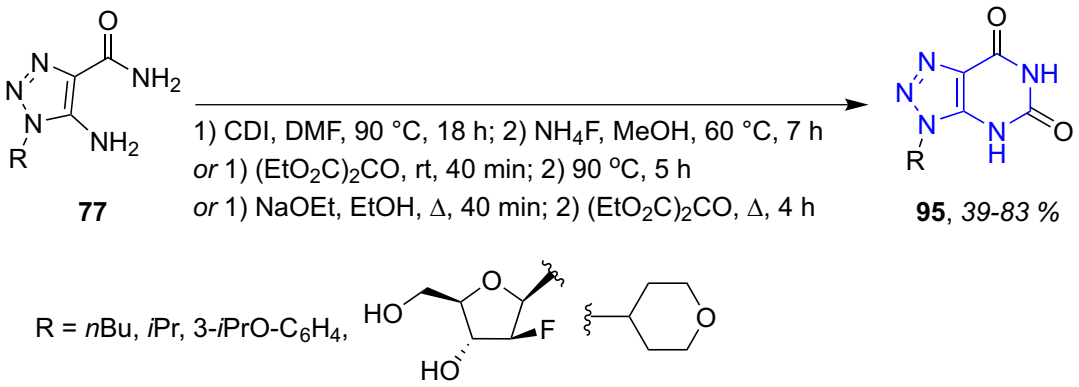
Heating of amides **90** with triethyl orthoacetate in the presence of acetic anhydride proved to be successful to obtain 6-alkyl(aryl)substituted triazolo[4,5-*d*]pyrimidines **91** (Scheme 28) [50].

The cyclocondensation of 5-aminotriazol-4-carbohydrazide **92** with an excess of triethyl orthoformate or triethyl orthoacetate led to ethyl-*N*-(triazolo[4,5-*d*]pyrimidin-6(7*H*)-yl)formimidates **93** undergoing the hydrolysis under acidic conditions to the corresponding 6-aminoderivatives **94** (Scheme 29) [54].

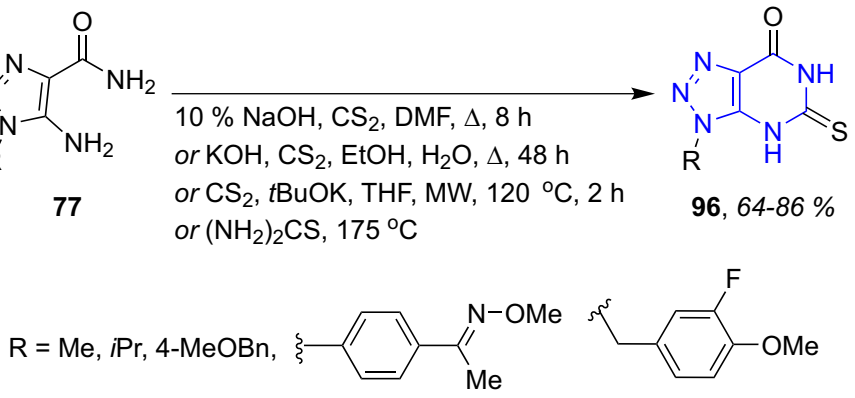
The synthesis of triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **95** was successful by heating triazolilaminoamides **77** with *N*,*N*'-carbonyldiimidazole (CDI) in DMF [6, 40, 47] or with diethyl carbonate in ethanol [55–60] (Scheme 30).

The condensation of aminoamides **77** with carbon disulfide under alkaline conditions [8, 34, 40, 61–63] or co-melting with thiourea [64] led to 3-substituted 5-thioxotriazolo[4,5-*d*]pyrimidine-7(4*H*)-ones **96** (Scheme 31).

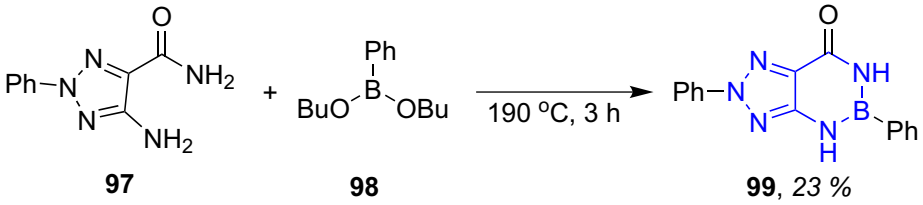
The high-temperature reaction of 5-amino-2-phenyltriazole-4-carboxamide (**97**) with dibutyl phenylboronate (**98**) turned out to be a convenient



Scheme 30. The synthesis of triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **95**



Scheme 31. The synthesis of 5-thioxotriazolo[4,5-*d*]pyrimidine-7(4*H*)-ones **96**



Scheme 32. The synthesis of triazolo[4,5-*d*][1,3,2]diazaborinin-7(4*H*)-one **99**

method for the preparation of triazolo[4,5-*d*]-[1,3,2]diazaborinin-7(4*H*)-one **99** (Scheme 32) [65].

2.3. The cyclocondensation of triazolilaminonitrites

Amidines or their salts **80** were used as 1,3-binucleophilic reagents to complete the pyrimidine ring to 5-aminotriazole-4-carbonitrile **100** in order to synthesize triazolo[4,5-*d*]pyrimidine-7-amines **101** (Scheme 33) [66].

A similar reaction of 5-(methylamino)triazole-4-carbonitrile **102** with acetimidate **80** produced 4-methyl-4*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-amine **103** (Scheme 34) [45].

A convenient method for the preparation of triazolo[4,5-*d*]pyrimidine-7-amine **105** was heating aminonitrile **104** in an excess of diethylmethylamine (DEMA) followed by the treatment with ammonia in MeOH (Scheme 35) [67].

The condensation of aminonitriles **106** with phenylisothiocyanate led to 7-anilinotriazolo[4,5-*d*]pyrimidine-5-thiones **107**, while **106** with potassium *O*-ethyldithiocarbonate or carbon disulfide followed by the treatment of the reaction mixture with methyl iodide yielded 5,7-*bis*(methylthio) derivatives **108** (Scheme 36). The intramolecular cyclocondensation of 5-cyano-4-ethoxymethyleneamino-1,2,3-triazoles **106** by 10 h reflux in NaHS solution proved to be convenient for the synthesis of triazolo[4,5-*d*]pyrimidine-7-thiones **109** [68].

The cyclization of 5-aminotriazole-4-carbonitrile **25** with phenylisocyanate, isothiocyanates, or thiourea at elevated temperatures was successfully used to obtain triazolo[4,5-*d*]pyrimidin-

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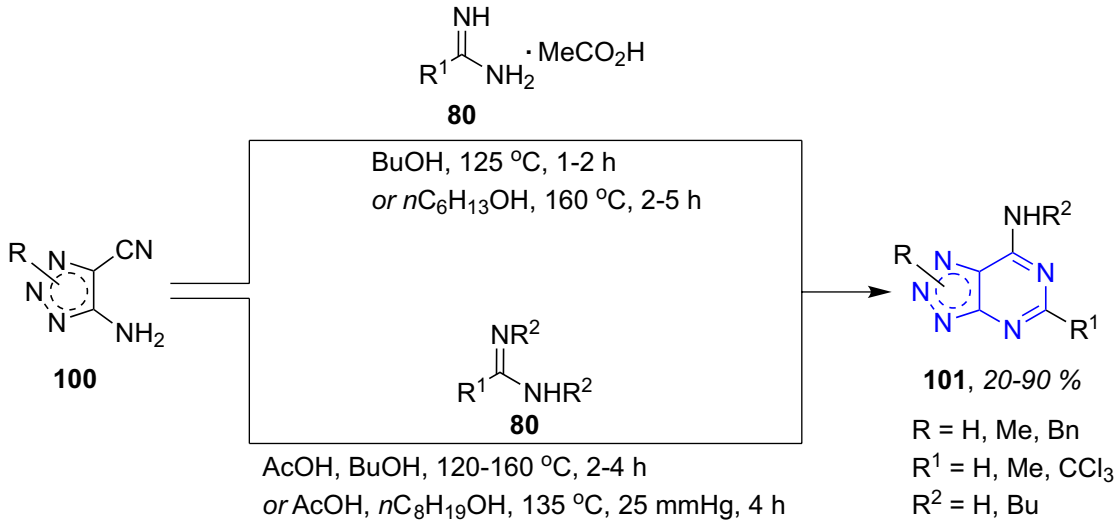
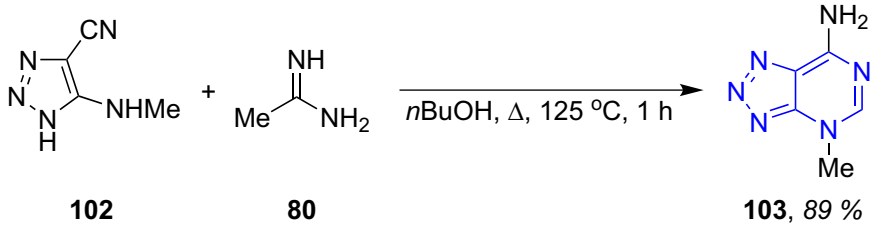
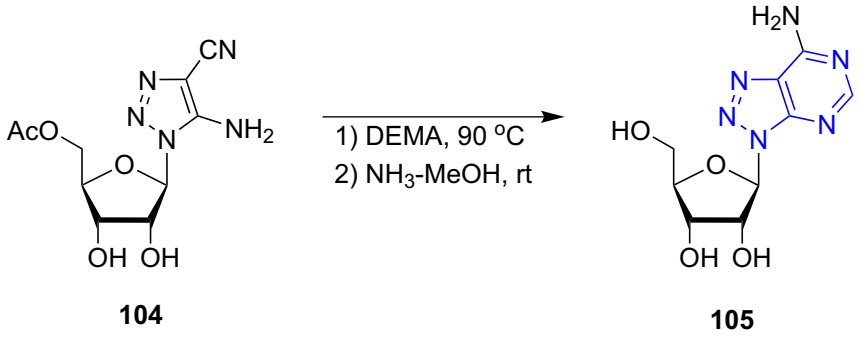


Scheme 33. The synthesis of 5-substituted triazolo[4,5-*d*]pyrimidine-7-amines **101**



Scheme 34. The synthesis of 4-methyl-4*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-7-amine **103**



Scheme 35. The synthesis of triazolo[4,5-*d*]pyrimidine-7-amine **105**

5-ones **110** and triazolo[4,5-*d*]thiones **111**, **112**, respectively (Scheme 37) [2].

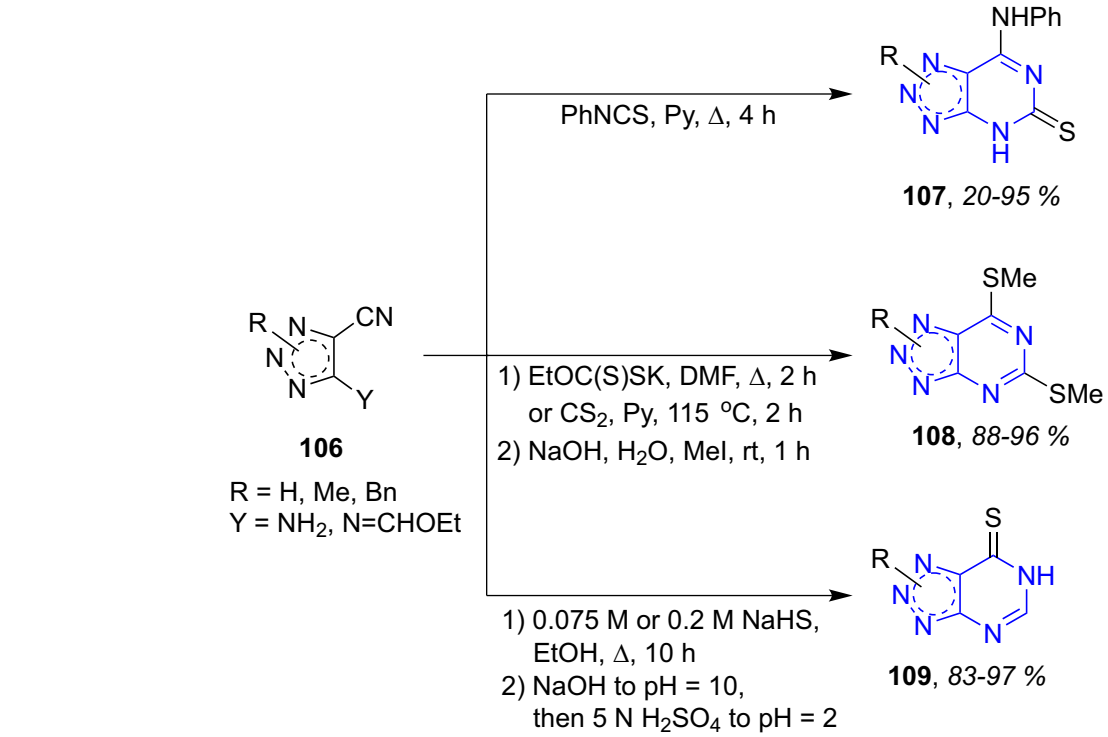
Isomeric 4-aminotriazole-5-carbonitrile **113** was subjected to the cyclization to triazolopyrimidine systems **114-116** in the reaction with formamide, phenylisothiocyanate, or carbon disulfide in an alcoholic solution of KOH. Its interaction with ethylenediamine formed imidazoyl-1,2,3-triazole **117**, which was converted to imidazo[1,2-*c*]-[1,2,3]triazolo[4,5-*e*]pyrimidine **118** by the action of triethyl orthoformate (Scheme 38) [69].

The authors of the work [70] successfully used the condensation of 4-hetarylsubstituted triazole-5-amines **120** (obtained from triazole-4-carbonitriles **119**) with orthoesters to synthesize imidazo-[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidines, pyrimido-[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidines, triazolo-[4',5':4,5]pyrimido[1,6-*a*][1,3]diazepines **121** (Scheme 39).

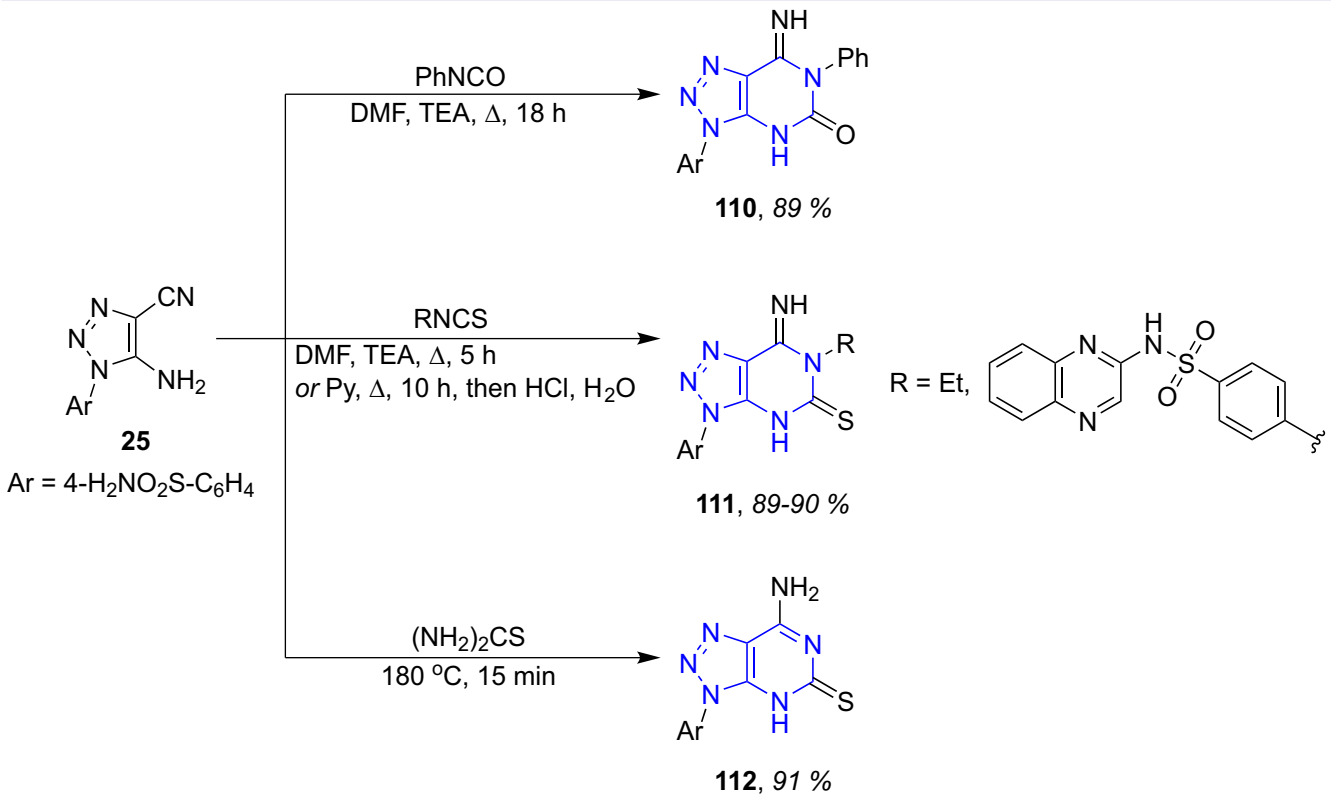
Hydrogenated analogs of imidazo[1,2-*c*][1,2,3]-triazolo[4,5-*e*]pyrimidines **122** were obtained by reacting imidazoyl-1,2,3-triazoles **120** with aromatic aldehydes (Scheme 39).

3. The synthesis of triazoloannulated pyridazines, oxazines and thiazines

Despite the relative ease of fusion of the pyridine and pyrimidine nuclei to the triazole ring, obtaining polycyclic systems with other heteronuclei proved to be a more difficult task. However, the authors of [71] succeeded in synthesizing 3*H*-[1,2,3]triazolo[4,5-*c*]cinoline **124** by the nitrosation



Scheme 36. Preparation of sulfur-containing triazolo[4,5-*d*]pyrimidines **107-109**



Scheme 37. The synthesis of triazolo[4,5-*d*]pyrimidin-5-(thi)ones **110-112**

of the amino group of 1,4-diaryl-substituted 5-aminotriazole **123** followed by the intramolecular azo coupling (Scheme 40).

The cyclocondensation of 1-heteryl-substituted 5-aminotriazole-4-carboxylic acid **125** with acetic anhydride proved to be effective for the preparation of the triazolo[4,5-*d*][1,3]oxazine-7-one derivative **126** (Scheme 41) [25].

The cyclization of sodium carbamodithioate **128** (synthesized from triazolodiamine **127**) with an excess of CS_2 yielded triazolo[4,5-*d*][1,3]thiazine-5-thione **129** (Scheme 42) [72].

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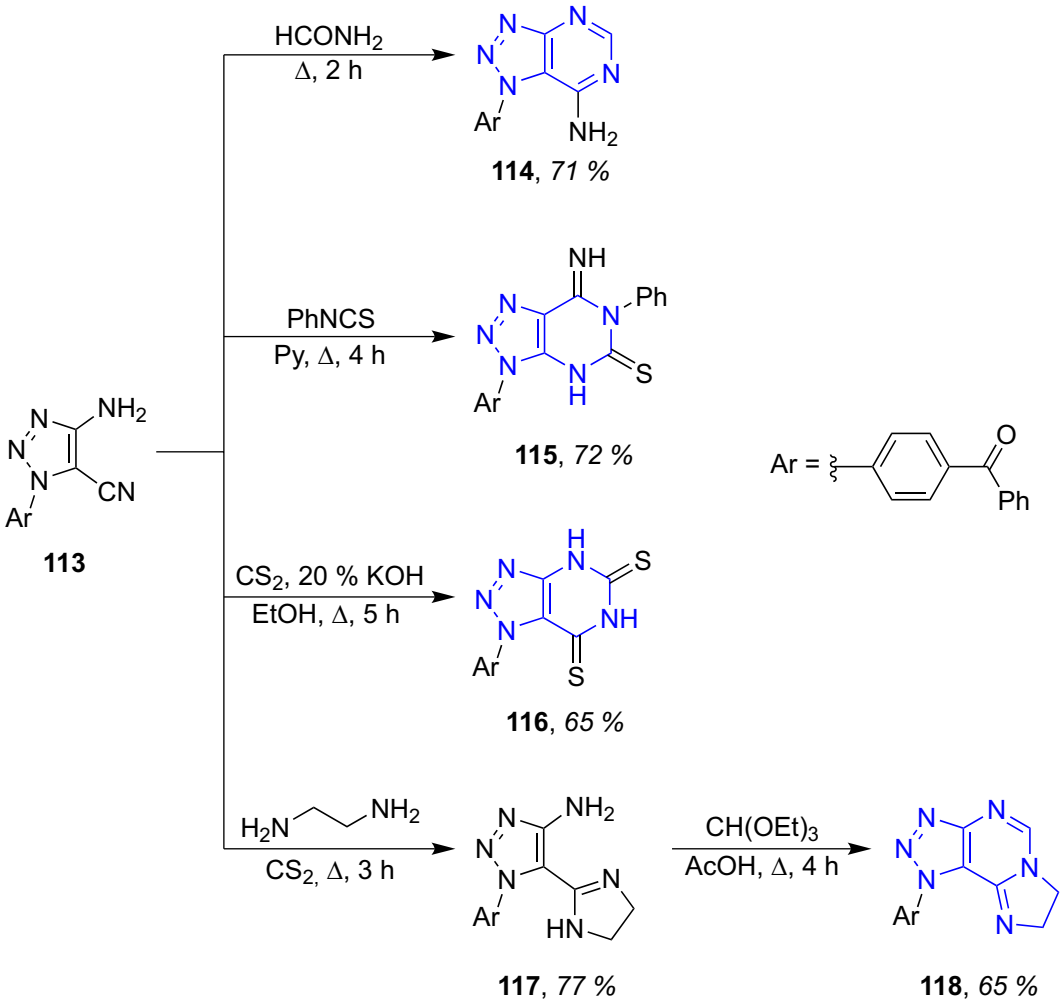
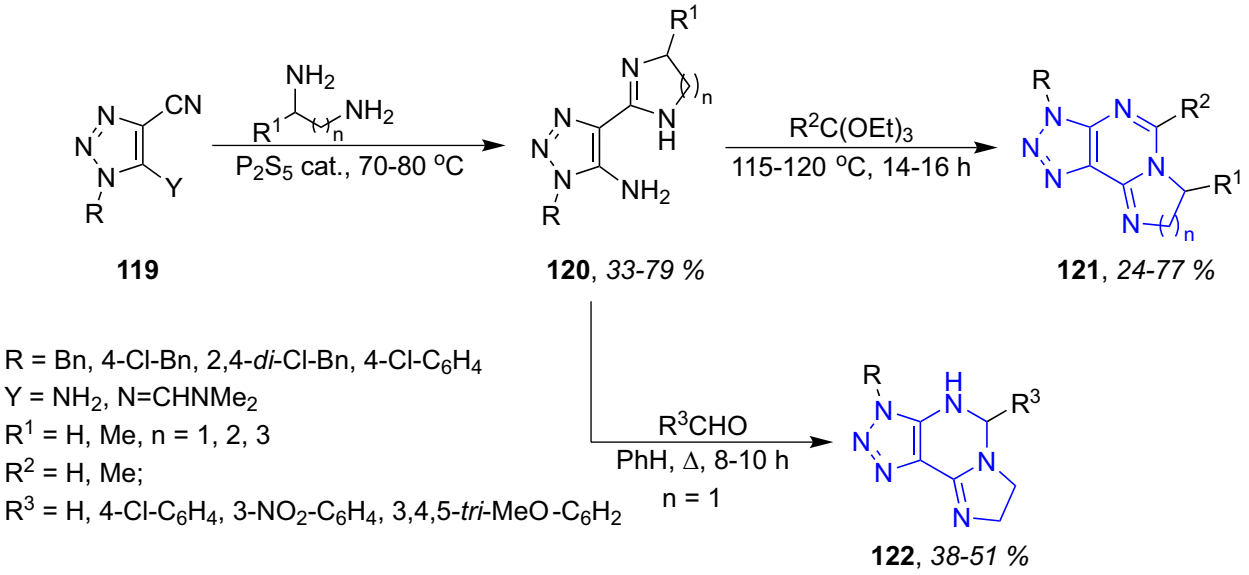
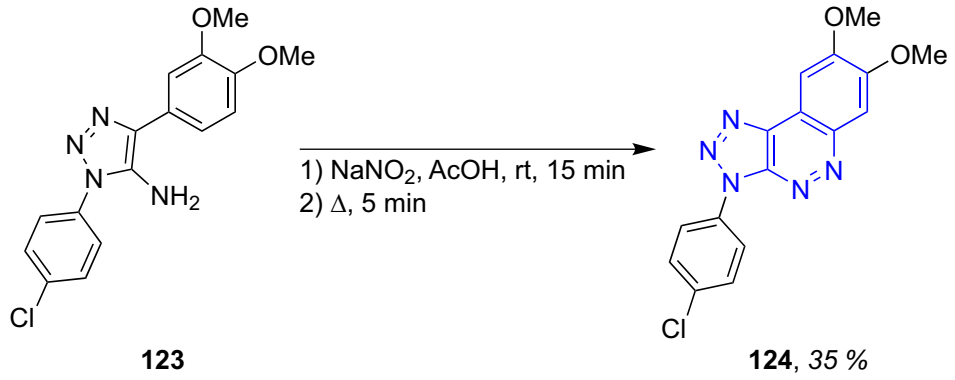


Scheme 38. The synthesis of bi- and tricyclic triazoloannulated pyrimidine systems

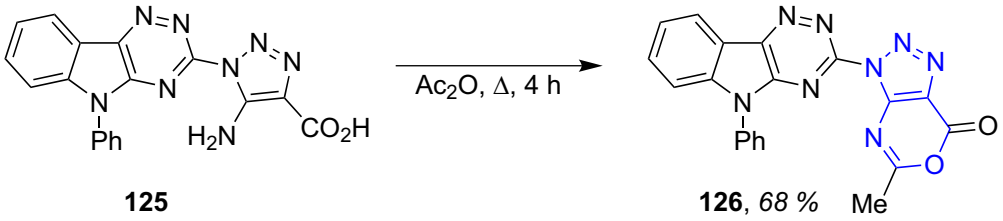


Scheme 39. The synthesis of tricyclic triazole-containing pyrimidines **121-122**



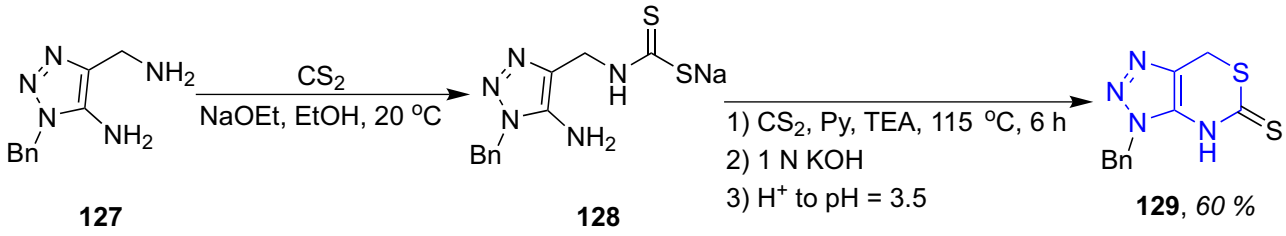
123 **124**, *35 %*

Scheme 40. The synthesis of 3*H*-[1,2,3]triazolo[4,5-*c*]cinoline **124**



125 **126**, *68 %*

Scheme 41. The synthesis of triazolo[4,5-*d*][1,3]oxazine-7-one **126**



127 **128** **129**, *60 %*

Scheme 42. The synthesis of triazolo[4,5-*d*][1,3]thiazine-5-thione **129**

4. The synthesis of triazoloannulated di-, oxa-, and thiazepines

In addition to the triazoloannulated azine structures described above, aminotriazoles also turned out to be important substrates for the synthesis of triazolodi(oxa-, thi)azepine systems.

The condensation of 4,5-diaminotriazoles **130** with β-dicarbonyl compounds proved to be a convenient tool for constructing a triazolo[4,5-*b*][1,4]-diazepine core with varying degrees of saturation (Scheme 43) [73]. Thus, a series of 1,5,7-substituted 1,6-dihydrotriazolo[4,5-*b*][1,4]diazepines **133** was obtained by the reaction of triazoles **130** with dibenzoylmethane, benzoylacetone and acetylacetone **131**. In turn, the reaction with ethyl acetoacetate and ethyl butyroacetate **133** proceeded through the step of forming enamino derivatives **134**, which were cyclized under basic conditions to 3,7-disubstituted triazolo[4,5-*b*][1,4]diazepin-5-ones **135**. In the case of benzoyl acetate **136**, the initially formed amides **137** were cyclized under acidic conditions to 1,7-disubstituted triazolodiazepin-5-ones **138**. Finally, 1,6-disubstituted triazolo[4,5-*b*][1,4]diazepine-5,7-diones **140** were obtained by the cyclocondensation of triazoles **130** with diethyl 2-methyl(2-phenyl)-malonate **139**.

For the synthesis of triazolo[4,5-*b*][1,5]benzodiazepines **144**, aminonitriles **141** were subjected to *N*-arylation with *ortho*-halogenonitrobenzenes **142** to derivatives **143**, their reduction and subsequent cyclization were done by the action of anhydrous $SnCl_2$ in an alcoholic solution of HCl (Scheme 44) [10, 74].

For the synthesis of optically active triazolo-[4,5-*d*][1,3]diazepin-8-oles **148** and **149**, *N*′-(4-formyltriazol-5-yl)-*N*,*N*-dimethylformimidates **145** were converted into trimethylsilylcyanohydrins **146**, then the reduction of the nitrile group with Raney nickel was accompanied by fusion of the diazepine ring and the formation of triazolodiazepine **147** (Scheme 45). The deprotection of the β-*D*-ribofuranosyl fragment and the subsequent chromatographic separation of racemates **147** yields target products with a high optical purity [75].

A convenient method for the synthesis of isoelectronic analogs of isoazepinomycin, triazolo-[4,5-*e*][1,4]diazepine derivatives, was developed

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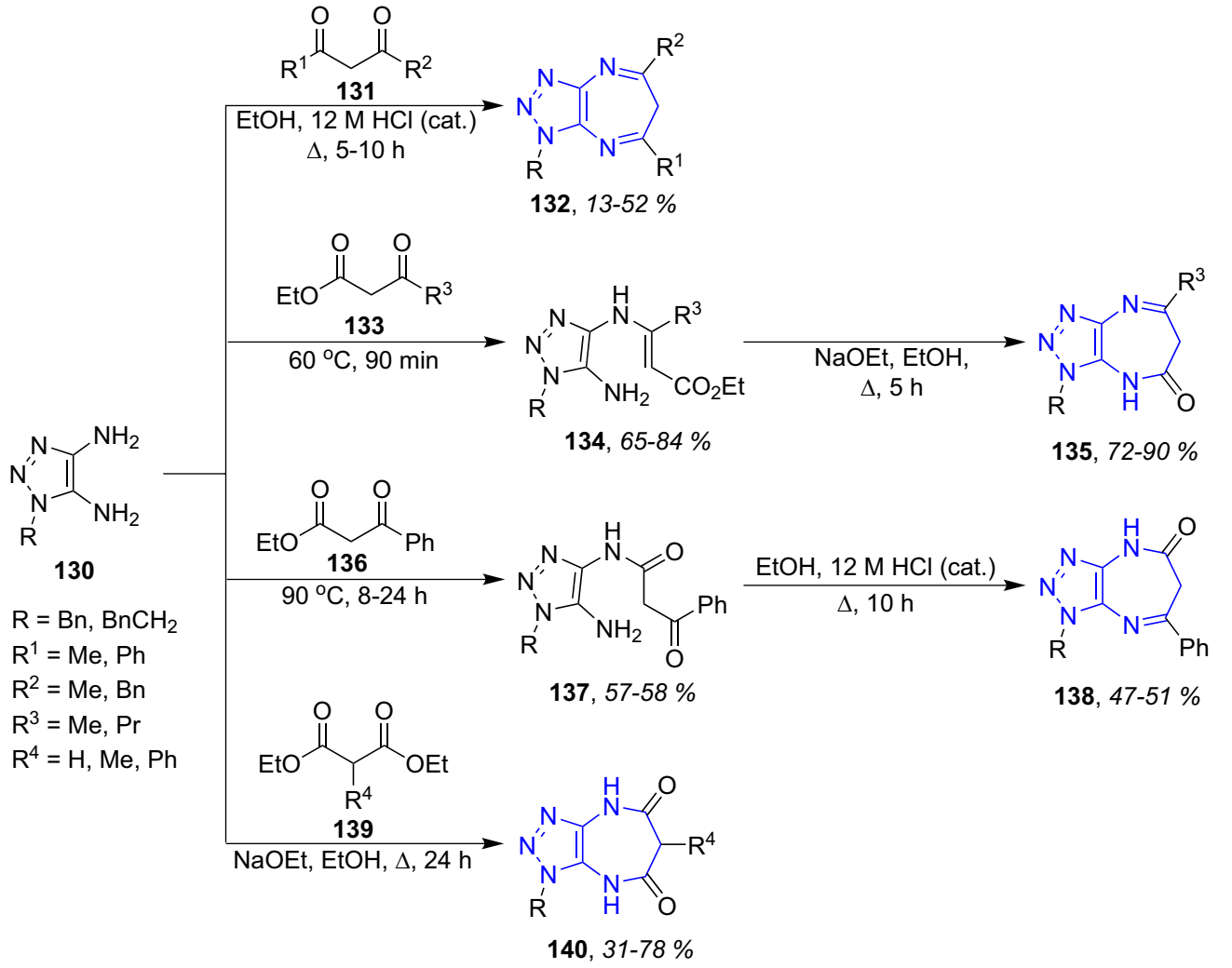
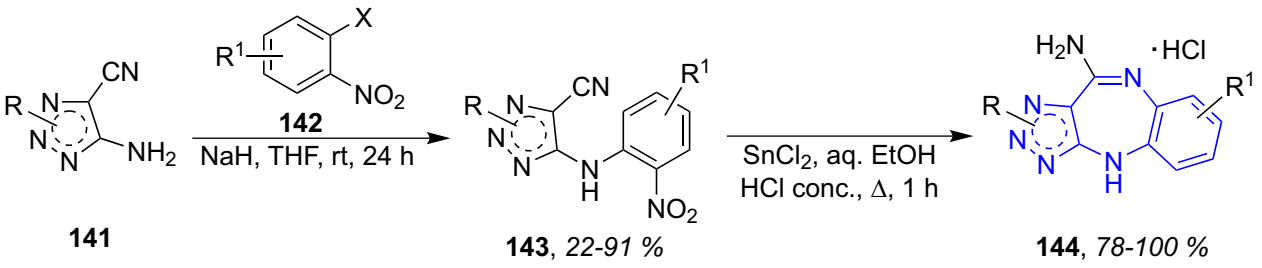


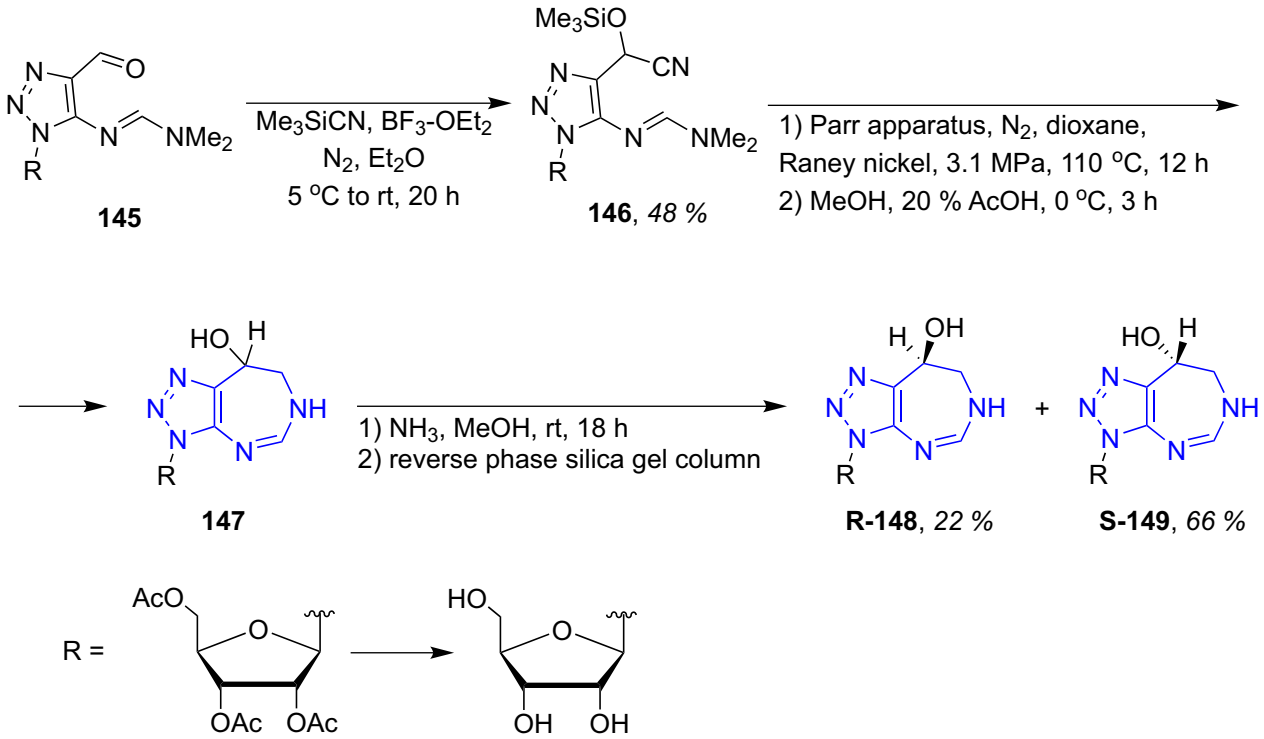
Scheme 43. 4,5-Diaminotriazoles **130** in the synthesis of triazolo[4,5-*b*][1,4]diazepines



Scheme 44. The synthesis of triazolo[4,5-*b*][1,5]benzodiazepines **144**

based on the intramolecular cyclization of *N*-functionally substituted aminotriazolocarboxamides **150** (Scheme 46). It was found that the latter were easily cyclized in formic acid at room temperature to 5-hydroxysubstituted triazolo[4,5-*e*][1,4]-diazepines **151** in almost quantitative yields. Under similar conditions, the action of *S*-nucleophiles **152** led to 5-sulfanylsubstituted triazolodiazepines **153**. It was most likely that in this reaction, the acid-catalyzed formation of the cyclic iminium intermediate **A** took place, to which the reagents containing the thiol group were then added [76].

N-Boc-4-amino-1,2,3-triazole-5-carboxylic acids **154** are a new type of bifunctional reagents. They were transformed into the corresponding amides **155** by the action of ethyl glycinate hydrochloride in the presence of a 2-fold excess of CDI (Scheme 47). Removal of the Boc-protection from their amino group by the action of an



145

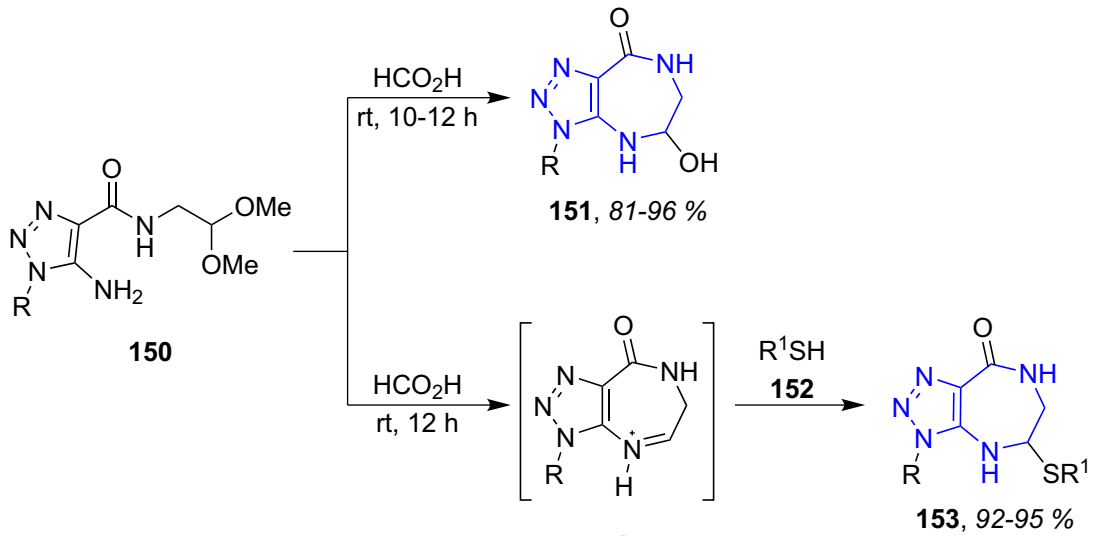
146, *48 %*

147

R-148, *22 %*

S-149, *66 %*

Scheme 45. The synthesis of triazolo[4,5-*d*][1,3]diazepin-8-oles **148**-**149** with optical purity



150

151, *81-96 %*

A

153, *92-95 %*

R = *i*Bu, Bn, 4-MeO-Bn, 3-Cl-Bn, Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 2,4-*di*-F-C_6H_3, 2,4-*di*-Me-C_6H_3, 1-methylpyrazol-3-yl

R^1 = CH_2CO_2H, CH_2CO_2Me, Ac, 4-Me-C_6H_4

Scheme 46. The synthesis of 5-hydroxy- та 5-sulfanylsubstituted triazolo[4,5-*e*][1,4]diazepines **151, 153**

equivalent amount of hydrogen chloride in dioxane at room temperature and the subsequent cyclocondensation by the action of NaOEt in the ethanol solution were optimal conditions for obtaining target triazolo[4,5-*e*][1,4]diazepine-5,8-diones **156** [77].

The authors of [78] used the reduction of amino ketones **157** using $NaBH_4$ to alcohols **158**; they proved to be convenient substrates for further transformations (Scheme 48). In particular, triazolooxazepinones **160** were obtained by the reaction of amino alcohols **158** with bromoacetyl bromide **159** followed by the cyclization under basic conditions. In turn, triazolothiazepinone **162** was synthesized by the cyclocondensation of aminoalcohol **158** with thioglycolic acid (**161**).

A selective *S*-alkylation of 4-(*N*-Boc-amino)-1,2,3-triazole-5-carbothioamides **163** with ethyl

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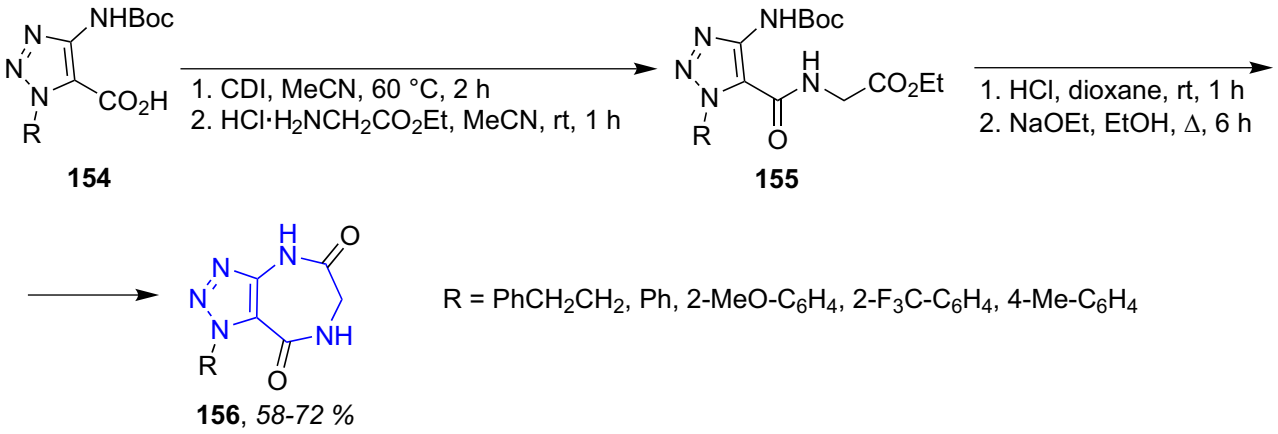
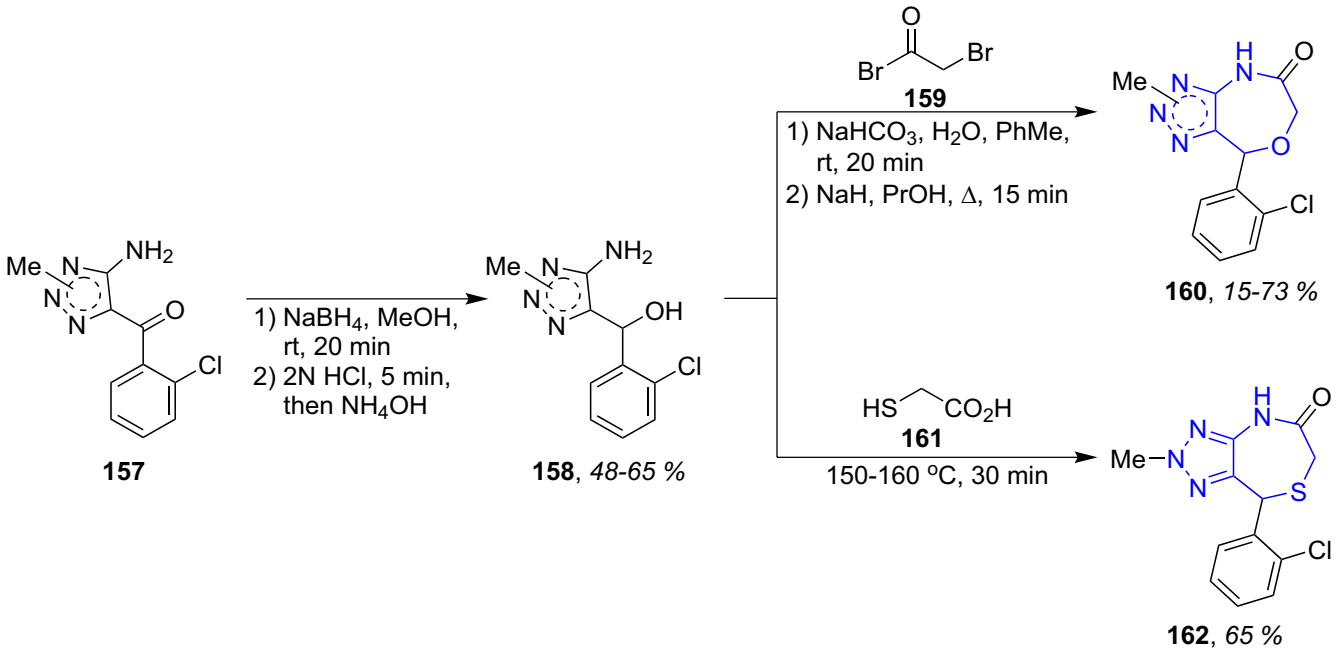
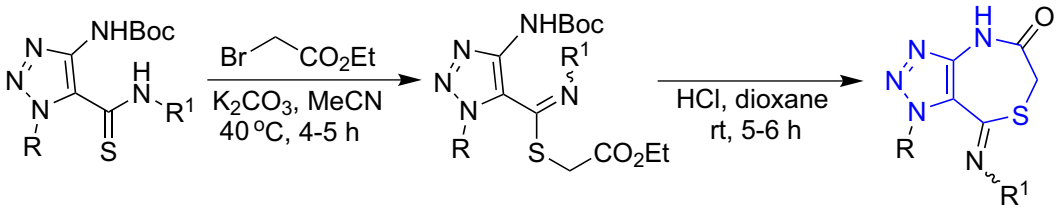


Scheme 47. The synthesis of triazolo[4,5-*e*][1,4]diazepine-5,8-diones **156**



Scheme 48. Preparation of triazolooxo- and triazolothiazepinones **160** and **162**



R = Me, R^1 = Et, *i*Pr, *t*Bu, cyclohexyl
R = CH_2CH_2Ph, R^1 = Et, *t*Bu
R = Ph, R^1 = Et, *t*Bu
R = 2-MeO-C_6H_4, R^1 = Et, *i*Pr

Scheme 49. The synthesis of [1,2,3]triazolo[4,5-*e*][1,4]thiazepin-5(6*H*)-ones **165**

bromoacetate under mild conditions led to the formation of 4-(*N*-Boc-amino)-5-thioimidates **164** (Scheme 49). The latter, when the protective Boc-group was removed by the action of hydrogen chloride in dioxane, underwent the intramolecular cyclocondensation with the formation of target [1,2,3]triazolo[4,5-*e*][1,4]thiazepin-5(6*H*)-ones **165** in high yields [79].

■ Conclusions

The analysis, systematization and generalization of literature sources related to the synthetic potential of 1,2,3-triazole-4(5)-amines convincingly indicate that structures of this type are easily accessible and convenient building blocks for the construction of triazoloannulated pyridine, azine and azepine systems that are important for synthetic and biomedical research.

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