UDC 547.791 + 547.82 + 547.853 + 547.782

N. O. Syrota¹, S. V. Kemskiy¹, L. M. Saliyeva², M. V. Vovk¹

¹ Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, 5, Murmanska str., Kyiv, 02098, Ukraine
² Lesya Ukrainka Volyn National University, 13, Voli Avenue, Lutsk, 43025, Ukraine

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]pyrimidines; triazoloannulated azepines; cyclocondensation
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 [2] and calcium/calmodulin-regulated kinases PIM [3], a potent antigen of the Dengue virus [4], were found in a number of triazoloaneled pyridines [4].

A low molecular weight agonist of cannabinoid receptor 2 (CB2) \( V \) [5], inhibitors of replication of the Chikungunya virus (CHIKV) [6] and a reversible inhibitor of lysine-specific demethylase 1 (LSD1) [7], compounds with the antitumor activity against breast cancer cells MCF-7, lungs A549 [8], and lungs H1650 [9] 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 antodopaminergic and anticholinergic activity to bind \([H]spiperone and [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)-amino triazoles 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]-1H-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]-1H-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)]-1H-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
Figure. The structures of the drug «Ticagrelor» I and bioactive triazoloannulated heterocycles II-X

Scheme 1. The synthesis of spirotriazolopyridones 4, 5
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(4H)-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-2H,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 dimethylacetel (DMFDM) 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-acetyltriazole-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).
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 triazolannulated pyridines 34 (Scheme 8) [18].

The authors [19] proposed effective conditions for the Friedlaender reaction 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-1H-[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...
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-arylaminosubstituted 1,2,3-triazolo-5-carboxylic acids 45 by their heating in polyphosphoric acid (Scheme 12).

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
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-1H-[1,2,3]triazolo[4,5-b]pyridine-6-carboxylic acids 40
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 amino-functionalized 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 with triethyl orthoformate gave the corresponding 5-ethoxy-methyleneamino-1,2,3-triazoles, which were easily cyclized to 6-aminotriazolo[4,5-d]pyrimidin-7-ones by the action of hydrazine hydrate (Scheme 13) [22]. Instead, the reaction of triazoles in the hydrazine solution after 3 h of boiling led to 5-amino-1,2,3-triazole-4-carboxhydrazides, which heterocyclization with triethyl orthoformate proved to be effective for obtaining (triazolo[4,5-d]pyrimidine-6-yl)formimidates.

In turn, the treatment of triazoles with an excess of primary amine in the presence of NH$_4$Cl at 200°C led to aminoamides, which upon prolonged heating with triethyl orthoformate yielded the target triazolo[4,5-d]pyrimidines.

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

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

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

A number of works 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 were converted by the action of Ph$_3$P into the corresponding iminophosphoranes.
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
The latter easily underwent aza-Wittig reaction with aromatic isocyanates to form triazolyl-containing carbodiimides 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 with a number of alkyllamines in the presence of NaOEt led to the selective formation of 5-alkylaminotriazolo[4,5-d]pyrimidin-7-ones (Scheme 18). At the same time, the formation of regioisomeric 5-arylaminoderivatives was observed under the action of ammonia or methylamine in the absence of a base.

The reaction of triazolylcarbodiimides with hydrazine hydrate in alcohol at room temperature also led to 5-arylamino-6-aminotriazolo[4,5-d]pyrimidin-7-ones (Scheme 19) [29].
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(6H)-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 monodicyclic acids [6, 40–45] (Scheme 23).

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

To build a pyrimidine ring based on 5-amino-4-triazolocarboxylic acid amidines 83 and to form 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].
Scheme 26. The synthesis of 1-methyltriazolo[4,5-d]pyrimidin-7-one 86

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

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

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 (NH₄)₂SO₄ 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-carboxyldrazide 92 with an excess of triethyl orthoformate or triethyl orthoacetate led to ethyl-N-(triazolo[4,5-d]pyrimidin-6(7H)-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(4H,6H)-diones 95 was successful by heating triazolilaminoamides 77 with N,N'-carbonyldimidazole (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(4H)-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
method for the preparation of triazolo[4,5-\textit{d}]-[1,3,2]diazaborinin-7(4\textit{H})-one 99 (Scheme 32) [65].

\textbf{2.3. The cyclocondensation of triazolilamino-nitriles}

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-\textit{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\textit{H}-[1,2,3]triazolo[4,5-\textit{d}]pyrimidine-7-amine 103 (Scheme 34) [45].

A convenient method for the preparation of triazolo[4,5-\textit{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-\textit{d}]pyrimidine-5-thiones 107, while 106 with potassium O-ethylidithiocarbonate 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-\textit{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-\textit{d}]pyrimidin-...
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, 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 hetero-nuclei proved to be a more difficult task. However, the authors of [71] succeeded in synthesizing 3H-[1,2,3]triazolo[4,5-c]cinoline 124 by the nitrosation...
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 carbamothioate 128 (synthesized from triazolidiamine 127) with an excess of CS, yielded triazolo[4,5-\(d\)][1,3]thiazine-5-thione 129 (Scheme 42) [72].

---

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

Scheme 39. The synthesis of tricyclic triazole-containing pyrimidines 121-122
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 triazolodioxa-, thiazepine systems.

The condensation of 4,5-diaminotriazoles 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 was obtained by the reaction of triazoles with dibenzoylmethane, benzoylacetone and acetylacetone [73]. In turn, the reaction with ethyl acetoacetate and ethyl butyrylacetate proceeded through the step of forming enamino derivatives, which were cyclized under basic conditions to 3,7-disubstituted triazolo[4,5-b][1,4]diazepin-5-ones [73]. In the case of benzoyl acetate, the initially formed amides were cyclized under acidic conditions to 1,7-disubstituted triazolodiazepin-5-ones [73]. Finally, 1,6-disubstituted triazolo[4,5-b][1,4]diazepine-5,7-diones were obtained by the cyclocondensation of triazoles with diethyl 2-methyl(2-phenyl)malonate [73].

For the synthesis of triazolo[4,5-d][1,3]oxazine-7-one, aminonitriles were subjected to N-arylation with ortho-halogenonitrobenzenes to derivatives, their reduction and subsequent cyclization were done by the action of anhydrous SnCl₂ 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 and 1,7-disubstituted triazolodiazepin-5-ones, N'-[(4-formyltriazol-5-yl)-N,N-dimethylformimidates were converted into trimethylsilylcyanohydrins, then the reduction of the nitrile group with Raney nickel was accompanied by fusion of the diazepine ring and the formation of triazolodiazepine (Scheme 45). The deprotection of the β-D-ribofuranosyl fragment and the subsequent chromatographic separation of racemates 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.
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
The 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 NaBH₄ 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
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

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

References


Boron-containing Analogs of Purine, Quinazoline 4, 345–349.

A. v-Triazolo[4,5-]


Information about the authors:

Natalia O. Syrota, engineer of the Department of Chemistry of Functional Heterocyclic Systems, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0001-8275-7514.

Sergiy V. Kemskiy, Ph.D. in Chemistry, researcher of the Department of Chemistry of Functional Heterocyclic Systems, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0003-4313-0991.

Lesya M. Saliyeva (corresponding author), Ph.D. in Chemistry, Senior Lecturer of the Department of Organic Chemistry and Pharmacy, Lesya Ukrainka Volyn National University; https://orcid.org/0000-0002-1047-8652; e-mail for correspondence: saliieva.lesia@vnu.edu.ua; tel. +380 95 4886559.

Mykhailo V. Vovk, D.Sc. in Chemistry, Professor, Corresponding Member of the National Academy of Sciences of Ukraine, Director of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0001-7739-670X.