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Chemistry

STRATEGIES FOR THE SYNTHESIS OF [1,2,4]TRIAZOLO[1,5-*a*]PYRIDINE-8-CARBONITRILES

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Abstract. Conjugated heterocyclic compounds with a 1,2,4-triazole core are of scientific interest due to their wide application in both synthetic and medicinal chemistry. In this review, we comprehensively summarize the synthetic methods for [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles. The methods are classified as follows: convertion of 8-substituted [1,2,4]triazolo[1,5-a]pyridines; synthesis based on functionalized pyridines, containing a nitrile group; synthesis based on heterocyclization of 2-(1,2,4-triazol-5-yl)acetonitriles, including cyclocondensation of 2-(1,2,4-triazol-5-yl)acetonitriles with β-dicarbonyl compounds and heterocyclization of 2-(1,2,4-triazol-5-yl)acetonitriles with α,β-unsaturated nitriles and esters; cyclocondensation of acyclic reagents, namely hydrazine derivatives and substituted methylenemalononitriles or their precursors and recyclization of oxadiazolopyridinium salts upon the interaction with ammonia or amine.

Keywords: aminopyridines, condensation, hydrazine derivatives, [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles, 2-(1H-1,2,4-triazol-5-yl)acetonitrile.

1. Introduction

The combination of various structural motifs with different biological activities in a single molecule plays an important role in medicinal chemistry. Cyanopyridines and 1,2,4-triazoles should be attributed to such structural motifs.[1] [1,2,4]Triazolo[1,5-a]pyridine-8-carbonitriles are well-known compounds exhibiting antibacterial[1-5] and antifungal[1,3,5-7] activities. Also, these compounds can serve as antioxidants with respect to 3 DPPH (2,2-diphenyl-1-picrylhydrazyl) and extend the lifespan of *Caenorhabditis elegans* displaying anti-inflammatory and antioxidant effects.[8,9] 7-[1-(*m*-Chlorophenyl)-3-(*p*-methoxyphenyl)-1*H*-pyrazol-4-yl]-5-oxo-2-*p*-tolyltriazolo[1,5-a]pyridine-6,8-dicarbonitrile shows high potential towards most human tumor cell lines and can be considered as a promising selective anticancer agent for further development of more potent anticancer drugs.[10] Substituted [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles were patented as PDE10 inhibitors[11] and immunomodulators.[12]

The rational design of some abovementioned prodrugs showed that position of cyano group in conjugated pyridine ring plays a crucial role in the biological activity of the title compounds.[6] On the other hand, it is well-known that nitrile group can be easily hydrolyzed. This property enforced scientists to use [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles as intermediates, particularly, for obtaining negative allosteric modulators of mGlu5.[13,14]

Heterocyclic compounds also exhibit a wide range of photo-physical properties. Reviewed compounds are not an exception. 2,5,7-Triaryl-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles have a great potential as fluorescent probes in medical application due to their strong blue fluorescence with large Stokes shifts and high quantum yields.[15,16]

The general synthetic strategies to the [1,2,4] triazolo[1,5-a]pyridine system have been summarized in reviews[17,18] and the recent advances in this field have been highlighted in the microreview.[19]

[1,2,4]Triazolo[1,5-a]pyridine-8-carbonitriles can be obtained from functionalized analogues of the readily-made [1,2,4]triazolo[1,5-a]pyridine system. The synthesis methods of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles are shown in Scheme 1. They include the replacement of the substituent at the position 8 with a CN group or by its transformation. This method allows to construct the conjugated system from compounds containing a nitrile group. The simultaneous generation of the two heterocyclic rings from acyclic reagents and recyclization of oxadiazolopyridinium salts upon the interaction with ammonia or amine action can also be performed.

Obtaining of the title 8-cyano-[1,2,4]triazolo[1,5-a]pyridines can be divided in five principle approaches.

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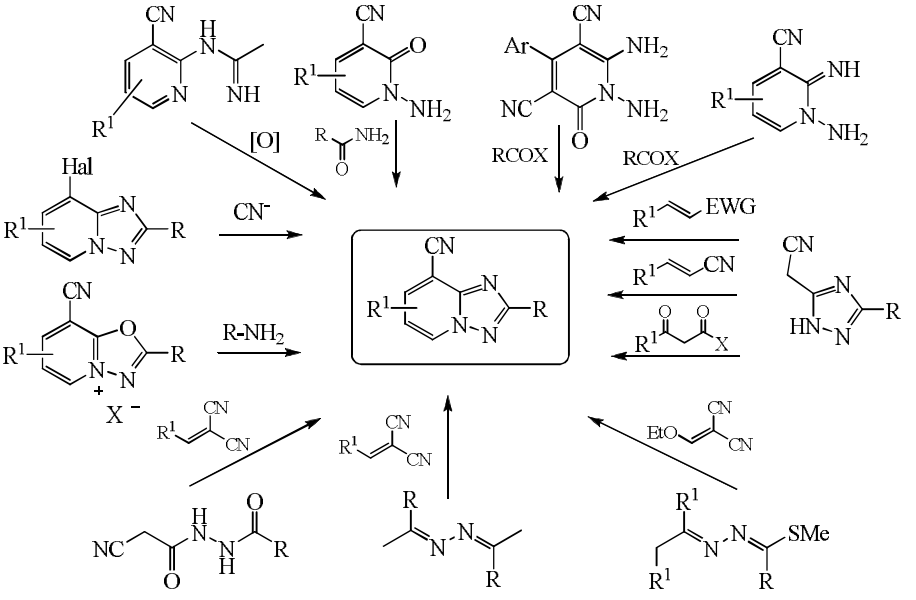
The first one is the introduction of the CN group into the ready-made heterocyclic system. The second and third ones are the construction of 1,2,4-triazole core from the pyridine precursor and *vice versa*. The fourth is the synthesis of the entire heterocyclic system starting from acyclic compounds. And the last one is followed by the change of the heteroatom to nitrogen in the precursor heterocyclic system.



Scheme 1. Strategies for the synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles

2. Synthesis from Functionalized Triazolo[1,5-a]pyridines

Some 8-substituted [1,2,4]triazolo[1,5-a]pyridines can serve as a source of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles through the transformation of a substituent at the 8-th position or its nucleophilic substitution. The intermediates for the negative allosteric modulators of mGlu5 **1** were prepared from 8-bromo-[1,2,4]triazolo[1,5-*a*]pyridines **2** by the substitution of bromine with CN group *via* a palladium-catalyzed reaction using zinc cyanide[13,14] (Scheme 2). 8-Bromo-6-chloro-[1,2,4]triazolo [1,5-*a*]pyridine **3** under the same conditions afforded **4a,b** after the preparative HPLC separation. These compounds were tested as PDE10 inhibitors (Scheme 2).[11]

Potassium hexacyanoferrate(II) trihydrate was used to convert 8-chloro derivative **5** in the presence of potassium acetate as a catalyst into [1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile **6**, patented as an immunomodulator (Scheme 2).[12] 8-Oxadiazolyl-[1,2,4]triazolo[1,5-a]pyridine **7** obtained by the cyclization of N-(pyridin-2-yl)formamide oxime **8** in hot polyphosphoric acid underwent transformation under heating to about 200 °C. Decomposition of the oxadiazolyl part to the nitrile resulted in [1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile **9** (Scheme 3).[20]

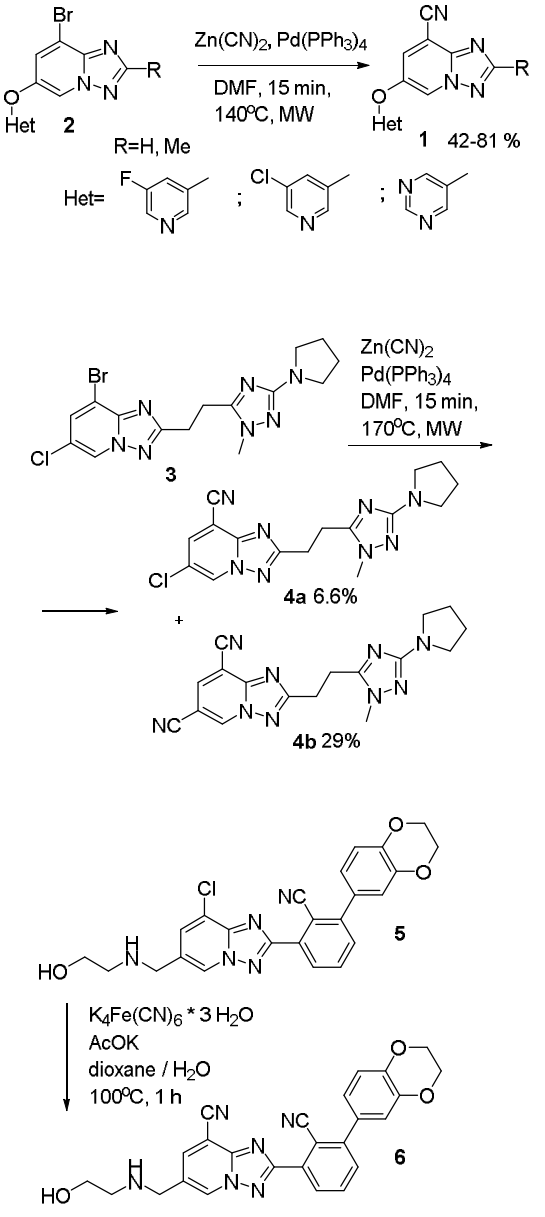
3. Synthesis Based on Functionalized Pyridines

A majority of conventional protocols are based on the using of available aminopyridines and their derivatives as the initial core to build the adjacent triazole. These precursors play various roles in the synthesis and depending on the second reagent can be considered as N-C-N, N-N-C or N-N-C-N component of the further 1,2,4-triazole fragment.

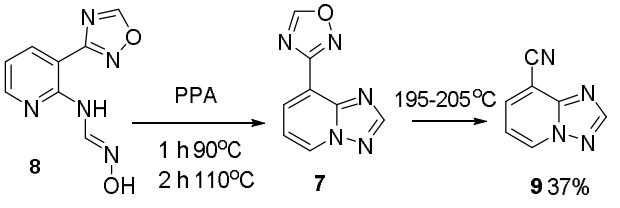
2-Amino-4-aryl-3-cyano-6-(2*H*-4-hydroxy-2-oxo-[1]benzopyran-3-yl)pyridines **10** were obtained starting from the chalcones of 4-hydroxycoumarins and malononitrile in the presence of ammonium acetate in alcohol, yielded 2-acetamidino-4-aryl-3-cyano-6-(2*H*-4-hydroxy-2-oxo-[1]benzopyran-3-yl)pyridines **11** upon the treatment with acetonitrile in the presence of $AlCl_3$. In this case the derivatives of 2-amino-pyridine can be considered as an N-C-N component. Oxidation of **11** by MnO_2 afforded 7-aryl-8-cyano-2-methyl-5-(2*H*-4-hydroxy-2-oxo-[1]benzopyran-3-yl)-[1,2,4]triazolo[1,5-a]pyridines **12** showing significant antibacterial and antifungal activities (Scheme 4).[1]

N-aminopyridine can serve as N-N-C component for the 1,2,4-triazole synthesis in one-pot cyclocondensation of 1-amino-3-cyano-4,6-dimethyl-2-pyridone **13,** prepared from cyanoacetohydrazide and acetylacetone,

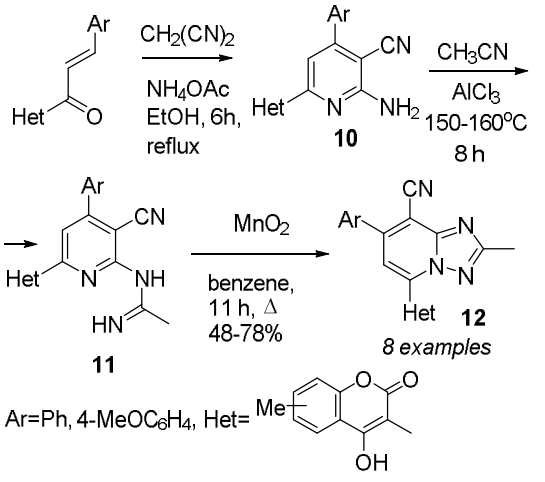
with carboxamides in the presence of anhydrous $ZnCl_2$, which afford triazolo[1,5-a]pyridines **14** in good yields (Scheme 5). This method appeared to be suitable for the aliphatic, aromatic and heterocyclic carboxamides.[21]



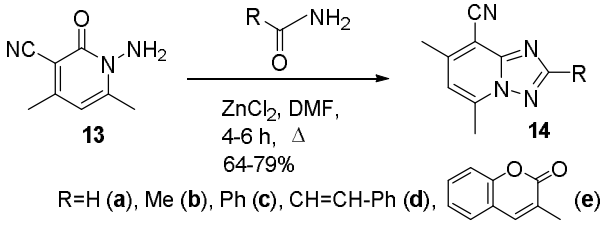
Scheme 2. Synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles from 8-halogeno analogues



Scheme 3. Synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile **9** under the decomposition of 8-oxadiazolyl-[1,2,4]triazolo[1,5-a]pyridine

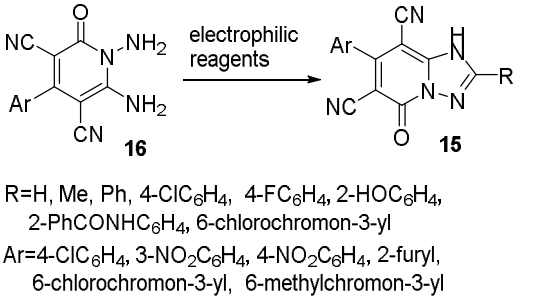


Scheme 4. Oxidative cyclization of N-(2-pyridyl)-amidines



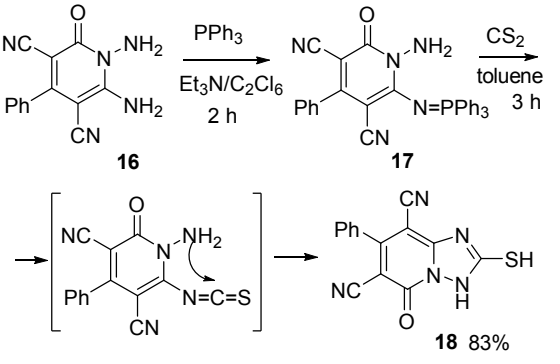
Scheme 5. Cyclocondensation of 1-amino-3-cyano-4,6-dimethyl-2-pyridone with carboxamides

The most common approach to obtain 5-oxo-1*H*-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **15** is the condensation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **16**. They can be easily prepared from arylidenemalononitriles and cyanoacetohydrazide, with a large number of mono electrophilic reagents, namely formic acid, ethyl formate, ethyl chloroformate, *N*-ethoxy-methylenebenzohydrazide, acetyl chloride and benzoyl chloride, acetic anhydride, carboxylic acid orthoesters, aromatic and heterocyclic aldehydes, carbon disulfide and 2-phenyl-4*H*-3,1-benzoxazin-4-one (Scheme 6). The literature data on this reaction up to 2014 is summarized in the review.[22] 1,6-Diamino-pyridines, like **16** can act as N-C-N-N building blocks in the reaction with carboxylic acid derivatives. According to the same procedure, 5-oxo-1*H*-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles can be obtained starting from 1,6-diamino-3,5-dicyano-4-(5-methylfuran-2-yl)-2-pyridone and appropriate aromatic and/or sugar aldehydes, ethyl acetoacetate and acetic acid/acetic anhydride, respectively,[23] as well as upon the reaction between 1,6-diamino-4-[1-(*m*-chlorophenyl)-3-(*p*-methoxyphenyl)-1*H*-pyrazol-4-yl]-2-oxopyridine-3,5-dicarbonitrile[10] or 1,6-diamino-4-(ethyllthio)-2-oxopyridin-3,5-dicarbonitrile[4] and substituted aromatic aldehydes.



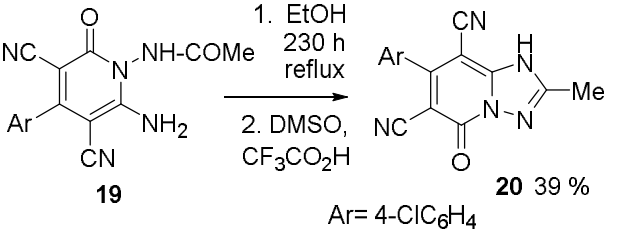
Scheme 6. Synthesis of 5-oxo-1*H*-4,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles from 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles

Reaction of 1,6-diaminopyridone **16** with triphenylphosphine provides 1-amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile-iminophosphorane **17**. **17**, in turn, reacted with carbon disulfide in a dry toluene to give 5-oxo-7-phenyl-2-thiol-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile **18** (Scheme 7).[24]



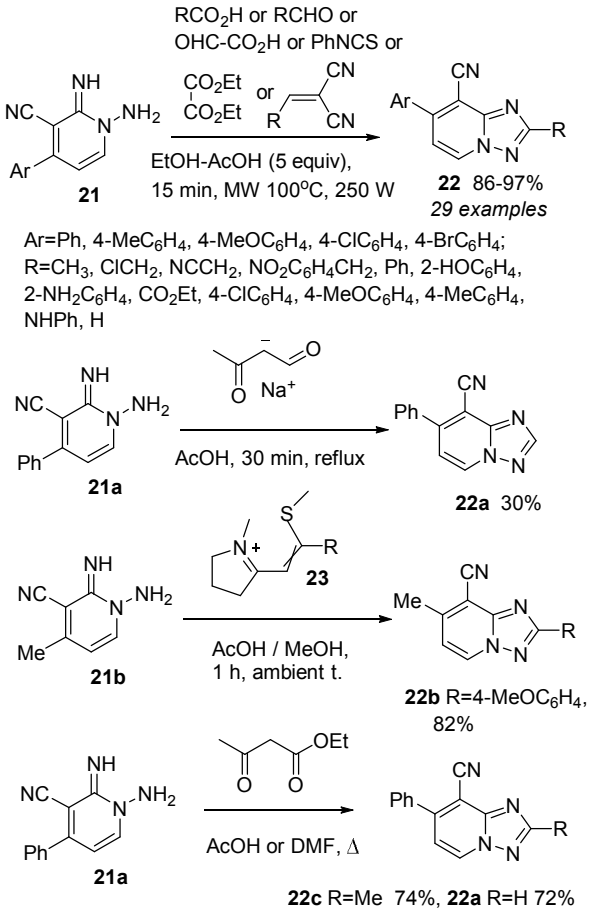
Scheme 7. Synthesis of 5-oxo-7-phenyl-2-thiol-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile

Heating of 1-acetamido-6-amino-4-(4-chlorophenyl)-2-oxo-2-dihydropyridine-3,5-dicarbonitrile (**19**) under reflux in the dry ethanol for 230 h, leads to intramolecular condensation producing triazolo[l,5-a]pyridine **20**, in 39 % yield (Scheme 8).[25]



Scheme 8. Cyclization of 1-acetamido-6-amino-4-(4-chlorophenyl)-2-oxo-2-dihydropyridine-3,5-dicarbonitrile

1-Amino-2-imino-1,2-dihydropyridin-3-carbonitriles **21** in the reaction with acetic acid derivatives yield [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles **22** (Scheme 9). Using of microwave irradiation speeds up the reaction efficiently.The reacton proceeded at a higher rate (15 min) and the yield is higher than with conventional heating (3 h).[26] A wide range of carboxylic acids and aldehydes (or their arylidene malononitriles), phenyl isothiocyanate, glyoxalic acid and acrylonitriles can be efficiently used for the synthesis of the corresponding derivatives *via* direct metal-free C–N bond construction (Scheme 9).[26] Formylacetone[27] or 2-aza-3-methylthio-propeniminium salt **23**[28] also react as acetic acid derivatives to form the corresponding [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles **22a** and **22b** (Scheme 9). Using of acetic acid or DMF as a solvent and $Pd(OAc)_2$ (10 mol %) as a catalyst, in the reaction of N-aminopyridine **21a** and ethyl acetoacetate leads to the formation of triazolo[1,5-a]pyridines **22c** (72 %) and **22a** (74 %). These substances presumably arise from the reaction between N-amino-2-iminopyridine **21** and either acetic acid or DMF (Scheme 9).[29]

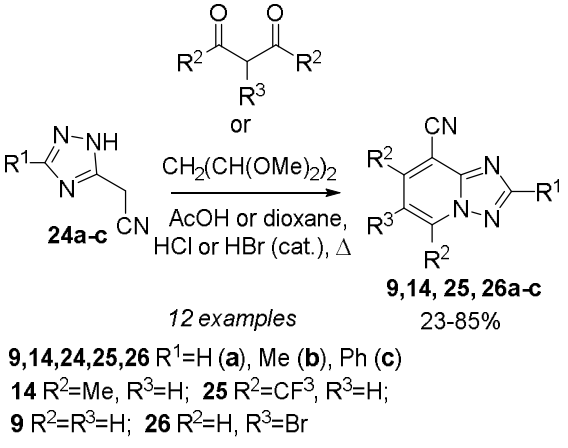


Scheme 9. Synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles based on 1-amino-2-imino-1,2-dihydropyridin-3-carbonitriles

4. Synthesis Based on the Heterocyclization of 2-(1,2,4-Triazol-5-yl)acetonitriles

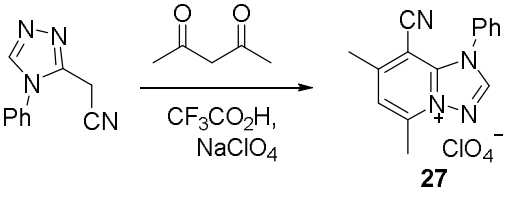
2-(1,2,4-Triazol-5-yl)acetonitriles are used in this strategy as the starting materials. They serve as the source of CN functional group and play the role of N-C-C component upon the construction of pyridine ring. Remaining C-C-C fragment originates from β-dicarbonyl compounds or α,β-unsaturated nitriles and esters.

Condensation of 2-(1*H*-1,2,4-triazol-5-yl)acetonitriles **24a-c** with β-diketones namely acetylacetone and hexafluoroacetylacetone proceeds smoothly in the presence of a catalytic amount of HCl in acetic acid under reflux for 1-4 h to furnish 5,7-dialkyl-[1,2,4]triazolo[1,5-*a*]pyridine-8-carbonitriles **14a-c** and **25a-c** in 57–85 % yields (Scheme 10).[30] Nitriles **24a-c** require less time to react with 1,1,3,3-tetramethoxypropane or 2-bromomalonic aldehyde, only 15 minutes are needed to form compounds **9a-c** and **26a-c**. The replacement of AcOH by dioxane in case of the product **9b** increases the yield.[30]



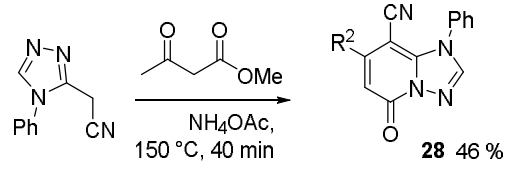
Scheme 10. Cyclocondensation of 2-(1,2,4-triazol-5-yl)acetonitriles with β-diketones and β-dialdehydes

Condensation of 2-(4-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile with acetylacetone in TFA in the presence of $NaClO_4$ results in triazolopyridinium salt **27** (Scheme 11).[31]



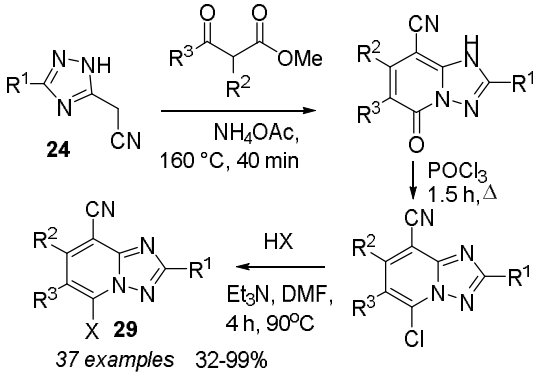
Scheme 11. Condensation of 2-(1,2,4-triazol-5-yl)acetonitriles with acetylacetone

The reaction of 2-(4-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile with ethyl acetoacetate and two equivalents of ammonium acetate, heated in an oil bath (150°C) over 40 min leads to 7-methyl-5-oxo-1-phenyl-5*H*-1,2,4-triazolo[1,5-*a*]pyridine-8-carbonitrile in 46 % yield (Scheme 12).[32]



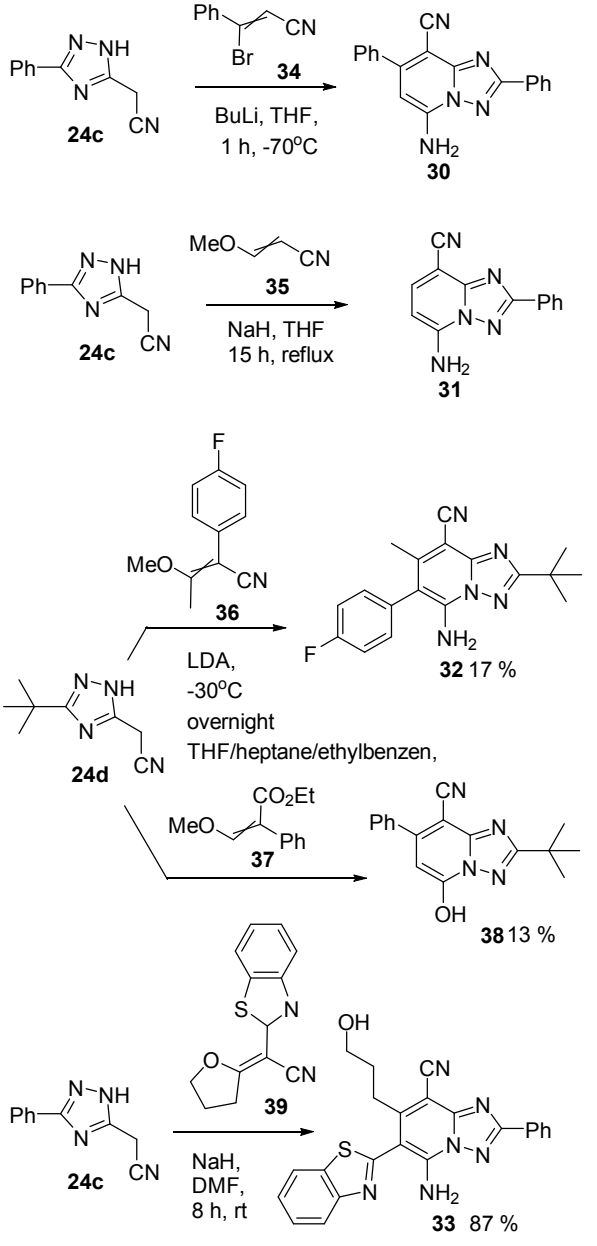
Scheme 12. Interaction of 2-(4-phenyl-4*H*-1,2,4-triazol-3-yl)-acetonitrile with ethyl acetoacetate

This method turned out to be common in obtaining of a significant number of [1,2,4]-triazolo[1,5-a]pyridine-8-carbonitriles **29** with a wide range of antifungal activity based on the functional mechanism of 1,6-inhibition of β-glucan synthesis. Compounds **29** are synthesized by cyclocondensation of 2-(1,2,4-triazol-5-yl)-acetonitriles **24** with β-keto esters in the presence of ammonium acetate, followed by $POCl_3$ treatment and subsequent amination (Scheme 13).[6,7]



Scheme 13. Synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles based on cyclocondensation of 2-(1,2,4-triazol-5-yl)acetonitriles with β-ketoesters

Heterocyclizations of 2-(1,2,4-triazol-5-yl)acetonitriles **24** with functionalized acrylonitriles in the presence of a strong base lead to 5-amino-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles **30-33** (Scheme 14).[7,33,34] Butyllithium is used as a base in the reaction of 5-phenyl-1*H*-1,2,4-triazole-3-acetonitrile **24c** with 3-bromo-3-phenyl-2-propenenitrile **34** to afford 5-amino-2,7-diphenyl[1,2,4] triazolo[1,5-a]pyridine-8-carbonitrile **30**. While 3-methoxy-2-propanenitrile (**35**) reacts with **24c** in the presence of NaH giving 5-amino-2-phenyl[1,2,4]triazolo-[1,5-a]pyridine-8-carbonitrile **31** (Scheme 14).[33]



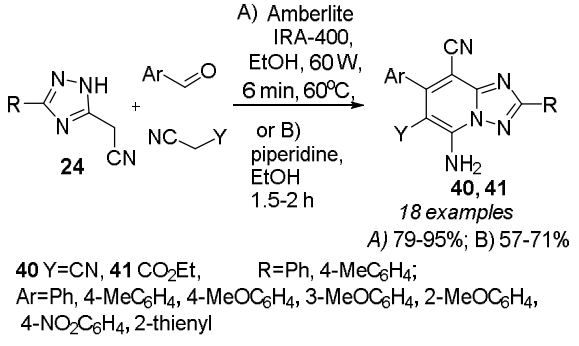
Scheme 14. Heterocyclizations of 2-(1,2,4-triazol-5-yl)acetonitriles with substituted acrylonitriles or acrylic esters

The reaction of 3-*tert*-butyl-5-cyanomethyl-1*H*-[1,2,4]triazole (**24d**) and 2-(4-fluorophenyl)-3-metho-

xybut-2-ene nitrile **36** is carried out with lithium diisopropyl amide in the mixture of tetrahydrofuran/*n*-heptane/ethylbenzene to yield 5-amino-2-*tert*-butyl-6-(4-fluorophenyl)-7-methyl[1,2,4]triazolo[1,5-a]-pyridine-8-carbonitrile (**32**). While the reaction with ethyl 3-methoxy-2-phenylacrylate (**37**) under the same conditions leads to 5-hydroxy derivative **38** (Scheme 14).[7]

A base promoted Michael addition of acetonitrile **24c** to the acrylonitrile fragment of 2-(benzothiazol-2-yl)-2-(tetrahydro-2-furanyliden)-acetonitrile **39** followed by ring transformations leads to 5-amino-6-(1,3-benzothiazol-2-yl)-7-(3-hydroxypropyl)-2-phenyl[1,2,4]triazolo [1,5-a]pyridine-8-carbonitrile (**33**), which is unequivocally confirmed by X-ray analysis (Scheme 14).[34]

An ultrasonic (60 W) promoted procedure for the multicomponent reaction of 2-(5-aryl-4*H*-1,2,4-triazol-3-yl)acetonitrile (**24**) with benzaldehides or thiophene-2-carbaldehyde and malononitrile or ethyl cyanoacetate (forming arylidene intermediate) using Amberlite IRA400 as a basic catalyst affords 5-amino-2-aryl-7-(het)aryl-6,8-dicarbonitriles **40** and ethyl 5-amino-8-cyano-2-aryl-7-(het)aryl[1,2,4]triazolo[1,5-a]pyridine-6-carboxylates **41** with the highest yield (79-95 %) in only 6 min. However, upon the classical heating conditions the reaction is carried out for 1.5 h with malononitrile and for 2 h with ethyl cyanoacetate (Scheme 15).[35]

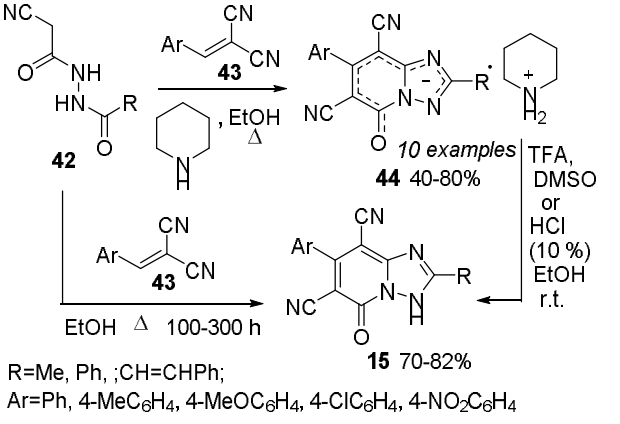


Scheme 15. Multicomponent reaction of 2-(5-aryl-4*H*-1,2,4-triazol-3-yl)-acetonitrile with aldehydes and malononitrile or ethyl cyanoacetate

5. Cyclocondensations of Acyclic Reagents

The simultaneous generation of two heterocyclic rings in the synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles is accomplished by combining of acyclic starting materials, namely hydrazine derivatives and substituted methylenemalononitriles or their precursors.

Michael addition of N'-acetyl(benzoyl, cinnamoyl)-2-cyanoacetohydrazides **42**, obtained from cyanoacetohydrazide by acylation, to benzylidene-malononitriles **43** followed by cyclization and aromatization leads to 6,8-dicyano-7-aryl-5-oxo-[1,2,4]triazolo[1,5-a]pyridines **15** (Scheme 16).[25]

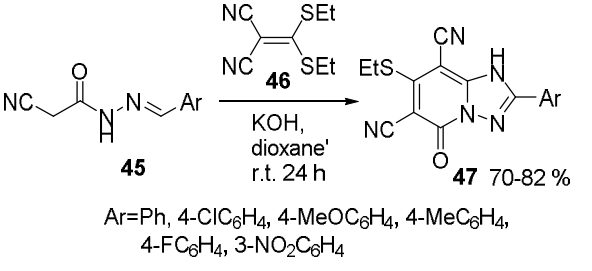


Scheme 16. Cyclocondensation of N'-acetyl(benzoyl, cinnamoyl)-2-cyanoacetohydrazides with benzylidenemalononitriles

In an attempt to accelerate the synthesis of **15** from **42** and **43** using piperidine as a basic catalyst, the piperidinium salts **44** with a piperidinium cation and delocalized conjugated heterocyclic anion were obtained, which was confirmed by X-ray analysis (Scheme 16).[25,36-38] Treatment of salt **44** with acid leads to the neutralization of this heterocyclic anion and the formation of triazolo[1,5-a]-pyridine **15** (Scheme 16).[25,37,38]

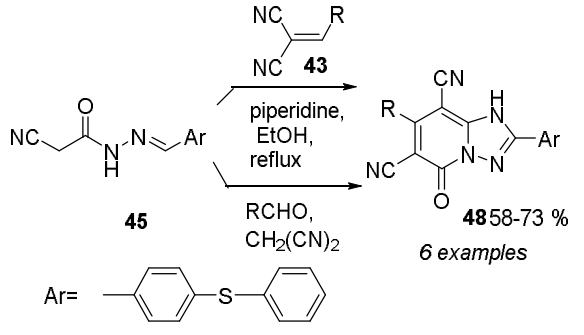
N'-[(aryl)-methylene]-2-cyanoaceto-hydrazides **45** can also be used as precursors for the synthesis of 5-oxo-2-aryl-3,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles by the reaction with some electrophilic reagents.

It is assumed that the reaction of N'-[(aryl)-methylene]-2-cyanoacetohydrazides **45** with 2,2-dicyanoethene-1,1-bis(ethylthiolate) **46** carried out in KOH-dioxane at room temperature for 24 h proceeds through intermediate Michael adducts, which cyclize to give the corresponding 7-(ethylthio)-5-oxo-2-aryl-3,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles **47** (Scheme 17).[4]



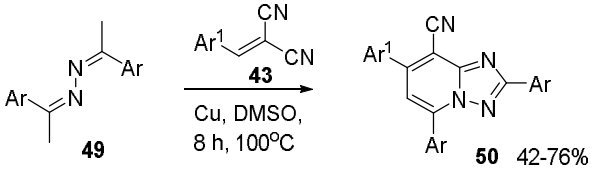
Scheme 17. Synthesis of 7-(ethylthio)-5-oxo-2-aryl-3,5-dihydro-[1,2,4]-triazolo[1,5-a]pyridine-6,8-dicarbonitriles

Treatment of hydrazone derivative **45** with arylidenemalononitriles **43** in the presence of piperidine as well as a ternary condensation of hydrazine **45**, an aromatic or aliphatic aldehyde, and malononitrile (1:1:1 molar ratio) in the presence of a basic catalyst furnishes the 5-oxo-1,2,4-triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **48** (Scheme 18).[5]



Scheme 18. Synthesis of 5-oxo-7-phenyl-2-(4-(phenylthio)phenyl)-3,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles

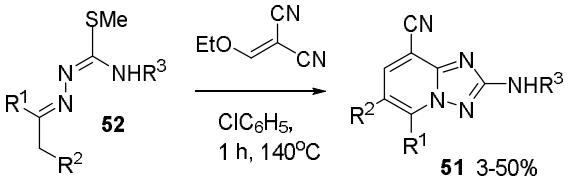
Copper-catalyzed tandem radical cyclization reaction of 1,2-bis(1-arylethylidene)hydrazines **49** with benzylidenemalononitriles **43** affords 2,5,7-triaryl-[1,2,4] triazolo[1,5-a]pyridine-8-carbonitriles **50** showing high potential as fluorescent probes in medical applications due to their strong blue fluorescence with large Stokes shifts and high quantum yields (Scheme 19).[15,16]



Ar=Ph, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 2-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-FC$_6$H$_4$, 3-BrC$_6$H$_4$, 3-MeOC$_6$H$_4$;
Ar^1=Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-BrC$_6$H$_4$, 3-MeC$_6$H$_4$

Scheme 19. Heterocyclization of 1,2-bis(1-arylethylidene)hydrazines with benzylidene-malononitriles

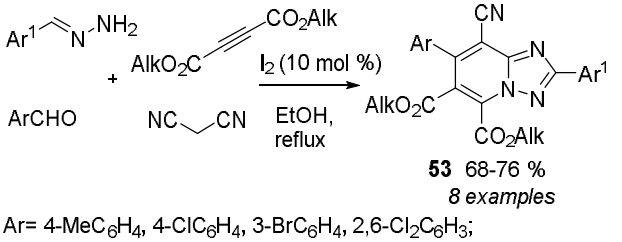
2-Alkylamino-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles **51** can be synthesized in moderate yields by cyclization of ketone isothiosemicarbazones **52** containing a bulky group at the terminal nitrogen and at least one α-methylene group, and ethoxymethylene-malononitrile with elimination of a thiol.[39] Butanone isothiosemicarbazone **52** (R^1=R^2=Me, R^3=*t*-Bu) gives an isomeric pair of 5-ethyl- and 5,6-dimethyl-triazolopyridines depending upon which the α-carbons are incorporated into the ring system, with the 5,6-dimethyl compound being the major product (Scheme 20).[39]



R^1=Me, R^2=H, Me, R^1-R^2=-(CH$_2$)$_3$-, -(CH$_2$)$_4$-
R^3=Et, *i*-Pr, *t*-Bu

Scheme 20. Cyclization of ketone isothiosemicarbazones and ethoxymethylene-malononitrile

8-Cyano[1,2,4]triazolo[1,5-a]pyridine-5,6-dicarboxylates **53** can be produced by simple one-pot procedure *via* pseudo five-component reactions between benzylidenehydrazines, dialkyl acetylene-dicarboxylates, benzaldehydes and malononitrile catalyzed by molecular iodine (Scheme 21).[40]

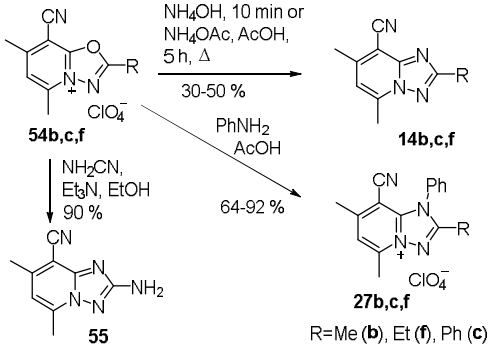


Ar= 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 2,6-Cl$_2$C$_6$H$_3$;
Ar^1=4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$; Alk=Me, Et

Scheme 21. Multicomponent synthesis of alkyl 8-cyano[1,2,4]-triazolo[1,5-a]pyridine-5,6-dicarboxylates

6. Recyclization of Oxadiazolopyridinium Salts upon the Interaction with Ammonia or Amine

8-Cyanooxadiazolopyridinium perchlorates **54b,c,f** undergo transformation into [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles **14b,c,f** upon treating with ethanolic ammonia or ammonium acetate in boiling acetic acid.[41] Subsequent heating with aniline gives the corresponding salts **27b,c,f**.[2] The reaction of **54b** with cyanamide results in 2-amino-5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyridine-8-carbonitrile **55** (Scheme 22).[42]



Scheme 22. Recyclization of 8-cyano- oxadiazolopyridinium salts under ammonia or amine action

7. Outlooks

[1,2,4]Triazolo[1,5-a]pyridine-8-carbonitriles are interesting for their biological activities and can be potentially applied as fluorescent agents. This review highlights advances in the synthetic methods for [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles by classifying them according to the types of reagents used. Many of the synthetic procedures used in the preparation of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles have been already known for a considerable time and are still in use today due to their efficiency and simplicity. Besides that new synthetic routes based on multicomponent reactions have been developed to reduce time and to increase the yields. It can be assumed that further study of the methods of synthesis of [1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles will expand their fields of application.

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СТРАТЕГІЇ СИНТЕЗУ [1,2,4]ТРИАЗОЛО [1,5-a]ПІРИДИН-8-КАРБОНІТРИЛІВ

Анотація. *Конденсовані гетероциклічні сполуки, що містять 1,2,4-триазольний цикл, становлять інтерес для науковців у зв'язку з їхнім широким застосуванням як у синтетичній, так і в медичній хімії. У цьому огляді вичерпно узагальнено методи синтезу [1,2,4]триазоло[1,5-а]піридин-8-карбонітрилів та класифіковано за типами використовуваних реагентів: перетворення 8-заміщених [1,2,4]триазоло[1,5-а]піридинів; синтези на основі функціоналізованих піридинів, що містять нітрильну групу; синтези на основі гетероциклізації 2-(1,2,4-триазол-5-іл)ацетонітрилів, ураховуючи циклоконденсації 2-(1,2,4-триазол-5-іл)ацетонітрилів з β-дикарбонільними сполуками та гетероциклізації 2-(1,2,4-триазол-5-іл)ацетонітрилів з α,β-ненасиченими нітрилами та естерами; циклоконденсації ациклічних реагентів, а саме похідних гідразину та заміщених метиленмалононітрилів або їхніх прекурсорів і рециклізацію солей оксадіазолопіридинію під дією аміаку або амінів.*

Ключові слова: *амінопіридини, конденсація, похідні гідразину, [1,2,4]триазоло[1,5-а]піридин-8-карбонітрили, 2-(1H-1,2,4-триазол-5-іл)ацетонітрил.*