Preprint Title	1,3-Dipolar cycloaddition of cyanopyridines to heterocyclic *N*-imines – combined experimental and theoretical studies
Authors	Aleksey Y. Vorobev, Gennady I. Borodkin, Rodion V. Andreev and Vyacheslav G. Shubin
Publication Date	20 Feb 2020
Article Type	Full Research Paper
Supporting Information File 1	ESI-TAZ-i.doc; 17.2 MB
ORCID® iDs	Aleksey Y. Vorobev - https://orcid.org/0000-0003-3346-4066; Gennady I. Borodkin - https://orcid.org/0000-0002-2691-9272; Rodion V. Andreev - https://orcid.org/0000-0003-1283-3627

1,3-Dipolar cycloaddition of cyanopyridines to heterocyclic *N*-imines – combined experimental and theoretical studies

Aleksey Yu. Vorob'ev*[1,2], Gennady I. Borodkin[1,2], Rodion V. Andreev[1] and Vyacheslav G. Shubin[1]

Address: [1]Novosibirsk Institute of Organic Chemistry, 9 Lavrentiev avenue, 630090 Novosibirsk, Russian Federation and

[2]Novosibirsk State University, 1 Pirogov street, 630090 Novosibirsk, Russian Federation

E-mail: Aleksey Yu. Vorob'ev - vor@nioch.nsc.ru

* Corresponding author

Abstract:

Series of 2-pyridyl substituted [1,2,4]triazolo[1,5-*a*]azines have been synthesized by reaction of cyanopyridines with *N*-aminoazinium mesitylenesulfonates under basic conditions. The reaction proceeds smoothly with pyridinium, 1,10-phenanthrolinium and 8-oxyquinolinium salts. In case of quinolinium and isoquinolinium salts dimers of corresponding *N*-imines were isolated. Pyrazinium- and pyridazinium-*N*-imines didn't possess any reactivity toward cyanopyridines. DFT studies give high activation barriers for 4-cyanopyridine cycloaddition to quinolinium and pyrazinium-*N*-imnes as well as highly negative free energy of dimerisation for quinolinium and isoquinolinium-*N*-imnes.

Keywords: DFT;1,3-dipolar cycloaddition; N-imines; [1,2,4]triazolo[1,5-*a*]azines

Introduction

[1,2,4]Triazolo[1,5-*a*]azines have attracted much attention from both medical chemistry and material science communities. Thus, [1,2,4]triazolo[1,5-*a*]pyridine scaffold was used in design of TDP2 [1], HIF PHD-1 [2], VEGFR-2 [3] and various types of JAK kinase [4,5] inhibitors. Furthermore, triazolo[1,5-*a*]pyridine derivatives GLPG0634 (filgotinib) and CEP33779 (Fig. 1) are highly selective inhibitors of Janus kinases type 1 and 2 respectively and are regarded as promising drug candidates. Also this heterocyclic unit was shown to be useful in design of host materials for high-performance red [6], white and RGB [7] or green [8] PhOLEDs. Similarly, [1,2,4]triazolo[1,5-*a*]pyrimidines, which chemistry recently was reviewed, have a broad spectrum of biological activity [9]. [1,2,4]Triazolo[1,5-*a*]pyrazines and quinoxalines was used in design of A_{2A} [10,11] and A_3 [12,13] adenosine receptors antagonists.

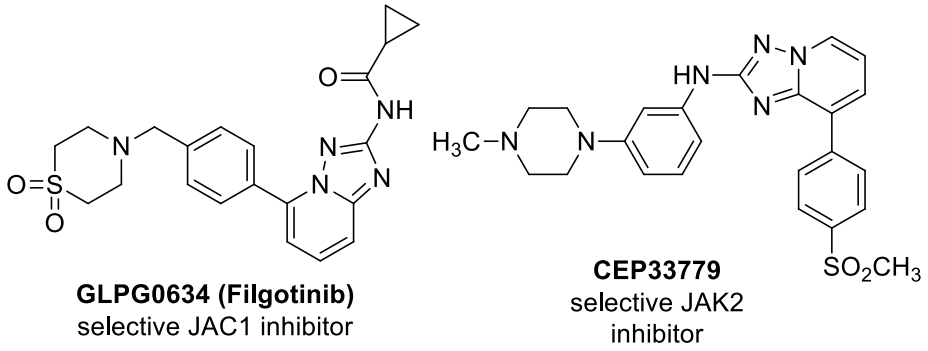


Figure 1. Medicinally important [1,2,4]triazolo[1,5-*a*]pyridines.

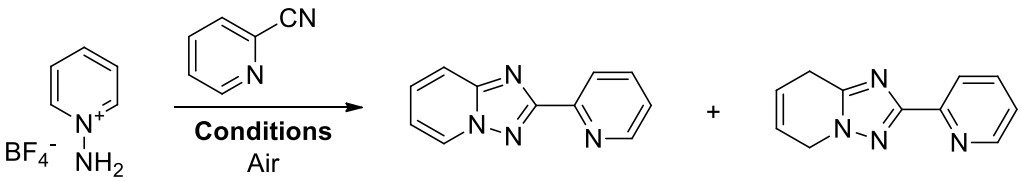
The practical significance of such scaffolds stimulated the development of viable synthetic methods for their preparation [9, 14]. One of the common approaches to [1,2,4]triazolo[1,5-*a*]azines is an oxidative cyclization of 2-pyridyl, pyrazinyl, pyrimidyl *etc.,* amidines or aminoguanidines to form N-N bond with various oxidants such as $Pb(OAc)_4$ [15], $PhI(OCOCF_3)_2$ [16], iodine [17], N-Cl reagents [18,19] or electrolysis [20]. During the past decade several catalytic procedures utilizing oxygen as oxidant and aminoguanidine [21] or 2-aminopyridine/nitrile[22] as starting materials were developed. Despite on their great potential these methods have significant limitation consisting in requirement of α-aminoazines as starting compounds. Other group of methods is based on *N*-aminoazinium salts, which are readily available by *N*-amination of parent azines with O-(mesitylenesulfonyl)hydroxylamine and related reagents [23]. 1,2-Diaminoazinium salts undergo cyclization with acid anhydrides or aldehydes [11, 24, 25] leading to corresponding triazoloazine. However, these salts also need in α-aminoazines for preparation. *N*-Aminopyridium salts readily give corresponding pyridinium-*N*-imines upon deprotonation. Such imines were known to react with nitriles to yield [1,2,4]triazolo[1,5-

a]pyridines [26,27]. This reaction was applied to synthesis of deuterated [28] or 2-aryl-substituted derivatives library for antifungal [29] and anticancer [30] activity screening. Recently our group employed the *N*-amination combined with nitrile cycloaddition for modification of commonly used ligands such as 8-oxyquinoline and 1,10-phenathroline [31]. The aim of this work is to study scopes of nitrile cycloaddition to various azine-*N*-imines. Cyanopyridines were chosen as model nitriles as obtained pyridyl substituted azoloazines could be of interest for coordination chemists.

Results and discussion

Initially, we applied previously described conditions [30] to pyridinium salt **1** and 2-cyanopyridine as model substrates (Table 1, entire 1). However, only poor yield of desired pyrazolopyridine **2a** was obtained. Noticeable amount of dihydropyrazolopyridine **3a** was also found in the reaction mixture. Then we screened effect of the base amount and solvent nature on the reaction yield. It turned out that increase of KOH equivalents from 1 to 5 (entries 2-5) led to rise in yield both **2a** and **3a** products. Further increasing of base quantity up to 10 eq (entry 6) didn't significantly affect on triazolopyridine **2a** output, however the amount of product **3a** was slightly decreased. The best results were achieved in H_2O as a solvent, although in EtOH similar results was obtained. However, it should be noted, that cyanopyridine should be added as solution in minimum amount of EtOH in case of multigram-scale reaction in view of worst solubility of cyanopyridines in water. Other solvent/base pairs tested (entries 10-12) didn't give satisfactory results. The cycloaddition reaction could proceed in ionic liquids as solvent (entries 13, 14), however the yields are low. Attempts of transition metals salts addition (entry 15) were unsuccessful. Next, we tried to oxidize product **3a** with different agents to improve the yield of **2a**. Unfortunately, such oxidants as chloranil, DDQ, bromine, H_2O_2 and MnO_2 led to full conversion of **3a** without formation of any definite product. On the other side, when oxygen was used, no oxidation of **3a** was found.

*Table 1. Conditions optimization of salt **1** reaction with 2-cyanopyridine.*



1 **2a** **3a**

Entry	Conditions	Yield of 2[a], %	Ratio 2:3[a]
1	1 eq KOH in H_2O/EtOH[b]	8	0.23
2	2 eq KOH in H_2O/EtOH	35	0.39
3	3 eq KOH in H_2O/EtOH	42	0.40
4	4 eq KOH in H_2O/EtOH	43	0.35
5	5 eq KOH in H_2O/EtOH	46	0.28
6	10 eq KOH in H_2O/EtOH	46	0.15
7	5 eq KOH in H_2O	48	0.13
8	5 eq K_2CO_3 in H_2O	0	-[c]
9	5 eq KOH in EtOH	45	0.06
10	5 eq K_2CO_3 in MeCN	25	-
11	5 eq CH_3ONa in CH_3OH	-	-
12	5 eq t-AmONa in tAmOH	11	-
13	5 eq KOH in BMIM BF_4	20	-
14	5 eq DBU in BMIM BF_4	25	-
15	5 eq KOH, $CuCl_2$ or CuCl (1% mol) in H_2O	-	-

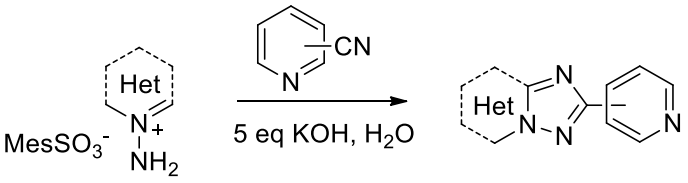
[a]The yields and product ratios were determined by ^1H NMR with CH_2Br_2 as internal standard

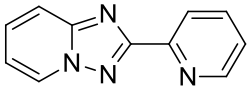
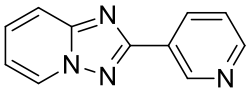
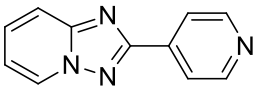
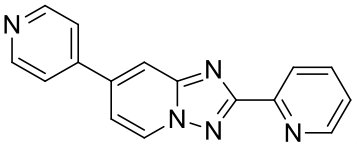
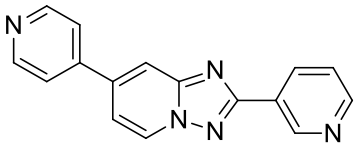
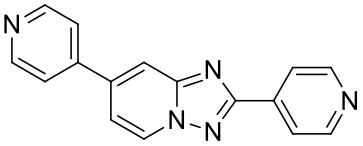
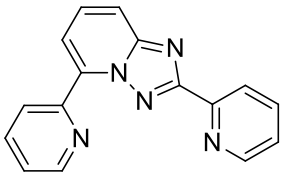
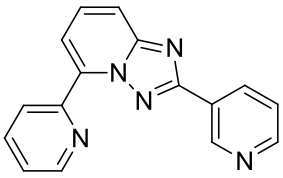
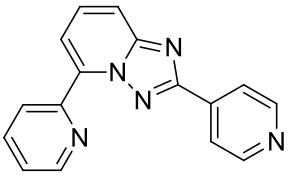
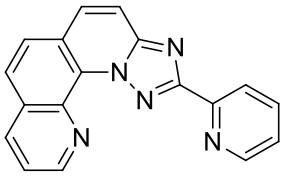
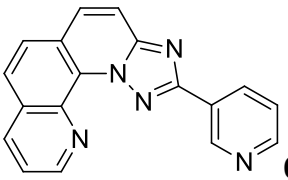
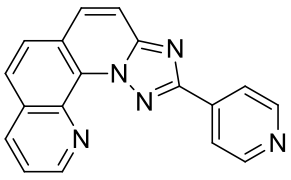
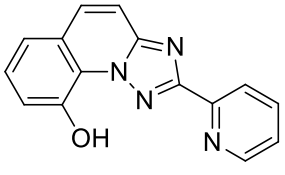
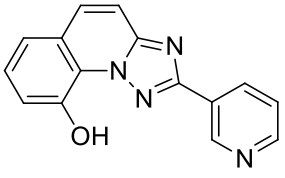
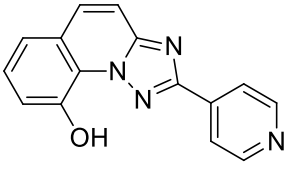
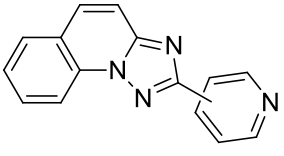
[b]Reaction was carried out at 0.1 mmol scale, 2N solution of bases in solvents were used.

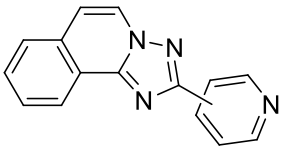
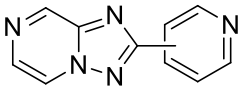
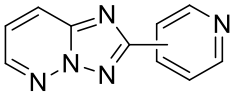
[c]No **3a** product was formed

With the optimized conditions in hand, the scope of this transformation was investigated. Both 3- and 4-cyanopyridines also readily reacted with N-aminopyridinium salt leading to corresponding triazolopyridines **2b,c** with nearly the same yields (Table 2). For 1-amino-4,4'-bipyridinium mesitylenesulfonate two conditions (entries 7,9 from table 1) were applied, and it was found that better results could be achieved in H_2O as a solvent, so such conditions were used in further studies. 1-Amino-2,2'-bipyridinium, 1-amino-1,10-phenanthrolinium and 1-amino-8-hydroxyquinolinium mesitylenesulfonates underwent 1,3-cycloaddition with cyanopyridines to form corresponding triazoloazines **4-7a-c** with satisfactory yields.

Table 2. Synthesis of [1,2,4]triazolo[1,5-a]azines.



Product	Yield, %[a]	Product	Yield, %[a]
 **2a**	48	 **2b**	49
 **2c**	43	 **4a**	70 (36[b])
 **4b**	36	 **4c**	51
 **5a**	36	 **5b**	39
 **5c**	44	 **6a**	42
 **6b**	66	 **6c**	50
 **7a**	57	 **7b**	54
 **7c**	51	 **8a-c**	traces

 **9a-c**	traces	 **10a-c**	0
 **11a-c**	0		

[a]Isolated yields; [b]Reaction was carried out in EtOH

In case of 1-aminoquinolinium and 2-aminoisoquinolinium mesitylenesulfonates insoluble solids were formed under standard reaction conditions. The solids were identified as dimers of corresponding *N*-imies according to NMR spectra. Previously such dimers were prepared from corresponding *N*-amino derivatives in basic media [32, 33]. Interestingly, that the quinilinium and isoquinolinium dimers reacted with a range of dipolarophiles yielding various heterocyclic products [33]. Our attempts to obtain products **8a-c** from quinolinium-*N*-imine dimer were unsuccessful and only traces of product were observed according to GC-MS and NMR. *N*-Amino derivatives of pyrazine and pyridazine didn't undergo the cycloaddition reaction, only corresponding *N*-imines, starting nitriles and nicotinamides were identified in the reaction mixtures by NMR. Such behavior may be explained by lower contribution of 1,3-dipolar structure **12a** to the resonance hybrid along with higher role of structure **12b** and, thus, low 1,3-dipolar character of *N*-imine (Fig. 2).

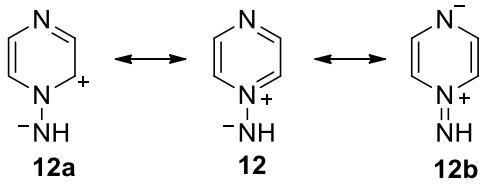


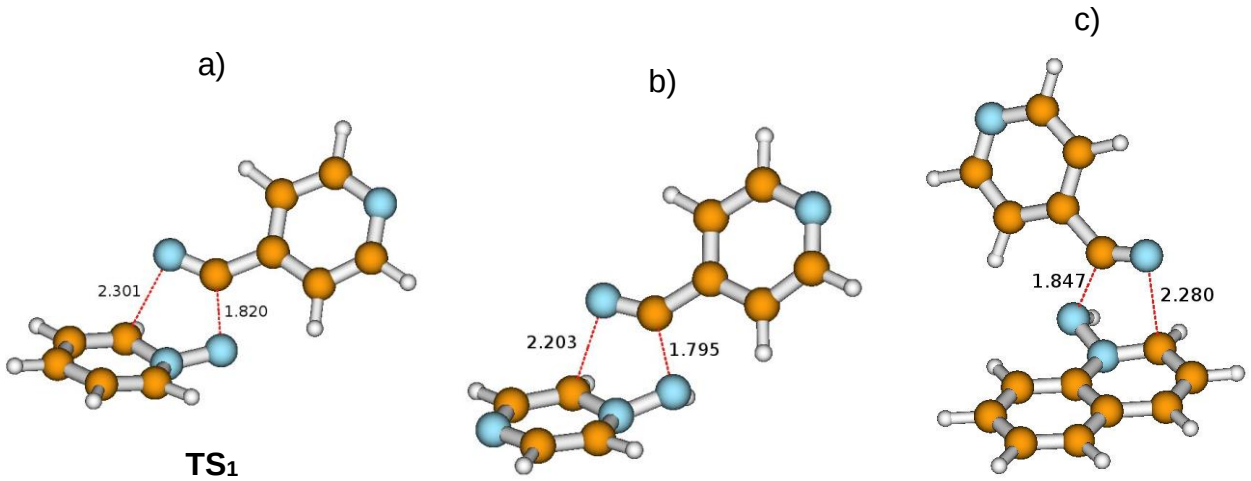
Figure 2. Dipolar resonance structures of pyrazinium-N-imine.

To get more insights into the reactivity of *N*-imines, DFT study (B3LYP/L1 level of theory with RI approximation and SMD solvation, see supporting information for details) of the process was performed. For cycloaddition of pyridinium-*N*-imine to 4-cyanopyridine transition state (**TS$_1$**) corresponding to concerted mechanism was localized (Fig. 3a). The geometry of **TS$_1$** is similar to previously reported transition state structures [34, 35] of dimethyl acetylenedicarboxylate to pyridinium-*N*-imines cycloaddition. However, in case of nitrile later transition state is realized according to shorter distance between pyridinium-N-imine and cyanopyridine. As shown on energetic diagram (Fig. 4), the reaction is slightly exothermic and cycloadduct **13** formed is much less stable than rearrangement product **14**, yet

mechanism of hydrogen atoms migration is unclear. According to reaction mechanism product **2c** is formed from adduct **13** by oxidation with air.

Pyrazinium-*N*-imine has slightly shorter N-N-bond (Fig. 3d) that reflects higher contribution of structure **12b** to the resonance hybrid (Fig. 2)**.** Also this imine has significantly lower HOMO level compared to pyridinium-*N*-imine, probably due to electron withdrawal properties of nitrogen atom. Thus, for pyrazinium-*N*-imine significantly increased activation energy was found in reaction with 4-cyanopyridine (Fig. 3b).

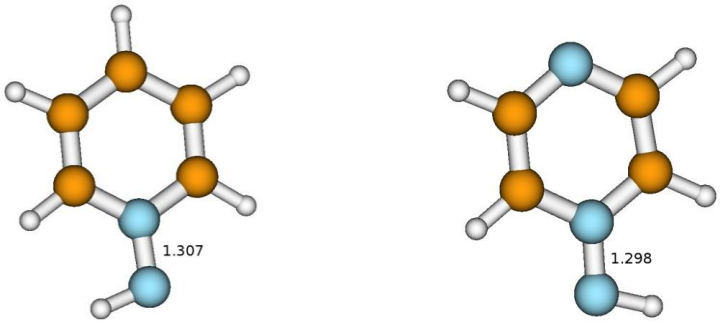
*Figure 3. Structures of transition states of nitrile cycloaddition to pyridinium (**a**), quinolinium (**b**) and pyrazinium-N-imines (**c**), and structures of pyridinium and pyrazinium-N-imines with their HOMO energy level (**d**).*



TS$_1$

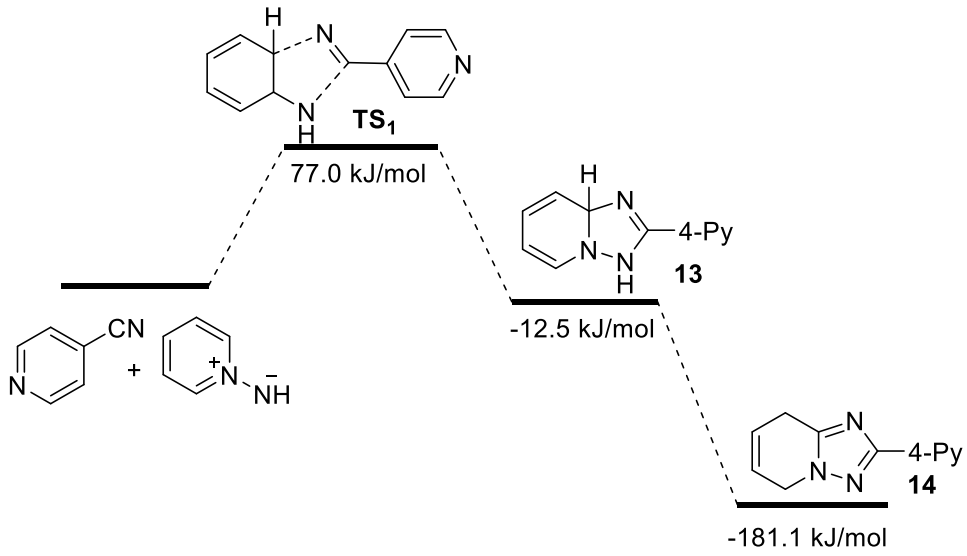
ΔG$^{\neq}$= 77.0 kJ/mol ΔG$^{\neq}$= 103.2 kJ/mol ΔG$^{\neq}$= 123.0 kJ/mol

d)



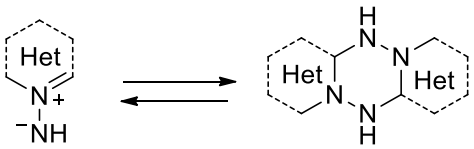
E(HOMO) = -0.1782 eV E(HOMO) = -0.2084 eV

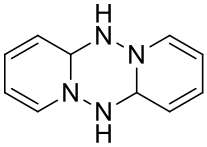
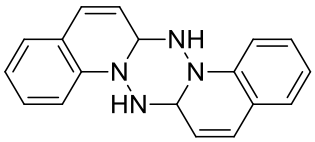
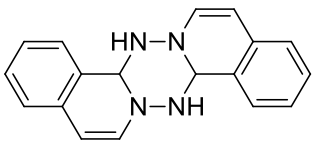
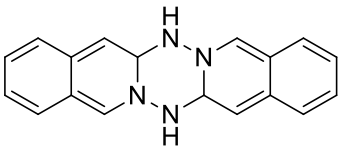
Figure 4. Energy diagram of 4-cyanopyridine to pyridinium-N-imine cycloaddition.

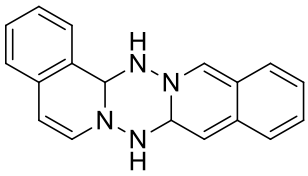
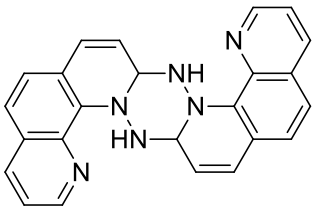
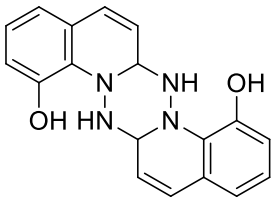
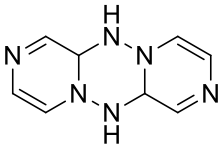


In case of quinolinium-*N*-imine substantially higher barrier was also observed. At the same time, dimerization of this imine is strongly favorable (Table 3). Even higher negative energy of dimerization was calculated for isoquinolinium-*N*-imine, and it is notably, that the most stable dimer formed by reaction at position 1 of the both rings. This is in accordance with the direction of nucleophilic attack in *N*-substituted isoquinolines. Pyridinium-, pyrazinium-*N*-imines and especially 1,10-phenanthrolinium-*N*-imine possess significantly more positive energy of dimerisation, so these imines have no dimerization as complicating factor.

Table 3. Calculated free energies of *N*-imines dimerization.



N-imine dimer	$\Delta_r G^o_{298}$, kJ/mol	*N*-imine dimer	$\Delta_r G^o_{298}$, kJ/mol
	-6.0		-67.8
	-73.8		3.0

	77.4		40.0
	-9.5		15.9

Conclusion

In summary, cycloaddition of cyanopyrirdines to various azinium-*N*-imines was studied. For pyridinium, 2,2'- and 4,4'-bipyridinium, 1,10-phenanthrolinium and 8-hydroxyquinolinium derivatives corresponding [1,2,4]triazolo[1,5-a]azines are formed under the air conditions. In case of qiunolinium- and isoquinolinium-N-imines their dimers were isolated as only products. Pyrazinium and pyridazinium imines didn't undergo both cycloaddition or dimerisation. Quantum chemical studies show high activation barriers for addition of 4-cyanopyridine to quinolinium and pyrazinium-*N*-inimes. Besides, quinolinium and isoqinolinium imines possess strong tendency to dimerization according to DFT studies.

Acknowledgments

Authors thank Multi-Access Chemical Research Center SB RAS for spectral and analytical measurements and Cluster of the Information Computation Center, Novosibirsk State University (http://www.nusc.ru/) for computing resources.

Funding

Authors thank Russian Science Foundation (project *№* 18-73-00133) for financial support.

Supporting information

Experimental procedures, computational details, characterization data and copies of ^{1}H and ^{13}C NMR spectra for obtained compounds and cartesian coordinates for DFT optimized structures.

Notes and references

1. Ribeiro, C. J. A.; Kankanala, J.; Xie, J.; Williams, J.; Aihara, H.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 257–261. https://doi.org/10.1016/J.BMCL.2018.11.044
2. Ahmed, S.; Ayscough, A.; Barker, G. R.; Canning, H. E.; Davenport, R.; Downham, R.; Harrison, D.; Jenkins, K.; Kinsella, N.; Livermore, D. G.; et al. *J. Med. Chem.* **2017**, *60*, 5663–5672. https://doi.org/10.1021/acs.jmedchem.7b00352
3. Ishimoto, K.; Fukuda, N.; Nagata, T.; Sawai, Y.; Ikemoto, T. *Org. Process Res. Dev.* **2014**, *18*, 122–134. https://doi.org/10.1021/op4002824
4. Siu, M.; Pastor, R.; Liu, W.; Barrett, K.; Berry, M.; Blair, W. S.; Chang, C.; Chen, J. Z.; Eigenbrot, C.; Ghilardi, N.; et al. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 5014–5021. https://doi.org/10.1016/j.bmcl.2013.06.008
5. Menet, C. J.; Fletcher, S. R.; Van Lommen, G.; Geney, R.; Blanc, J.; Smits, K.; Jouannigot, N.; Deprez, P.; van der Aar, E. M.; Clement-Lacroix, P.; et al. *J. Med. Chem.* **2014**, *57*, 9323–9342. https://doi.org/10.1021/jm501262q
6. Song, W.; Gao, L.; Zhang, T.; Huang, J.; Su, J. *J. Lumin.* **2019**, *206*, 386–392. https://doi.org/10.1016/J.JLUMIN.2018.09.006
7. Song, W.; Shi, L.; Gao, L.; Hu, P.; Mu, H.; Xia, Z.; Huang, J.; Su, J. *ACS Appl. Mater. Interfaces* **2018**, *10*, 5714–5722. https://doi.org/10.1021/acsami.7b18202
8. Song, W.; Chen, Y.; Xu, Q.; Mu, H.; Cao, J.; Huang, J.; Su, J. *ACS Appl. Mater. Interfaces* **2018**, *10*, 24689–24698. https://doi.org/10.1021/acsami.8b07462
9. Fischer, G. *Adv. Het. Chem.* **2019**, *128*, 1–101. https://doi.org/10.1016/bs.aihch.2018.10.002
10. Dowling, J. E.; Vessels, J. T.; Haque, S.; Chang, H. X.; Van Vloten, K.; Kumaravel, G.; Engber, T.; Jin, X.; Phadke, D.; Wang, J.; Ayyub, E.; Petter R. C. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 4809–4813. https://doi.org/10.1016/j.bmcl.2005.07.052
11. Yao, G.; Haque, S.; Sha, L.; Kumaravel, G.; Wang, J.; Engber, T. M.; Whalley, E. T.; Conlon, P. R.; Chang, H.; Kiesman, W. F.; Petter R. C. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 511–515. https://doi.org/10.1016/j.bmcl.2004.11.062
12. Catarzi, D.; Varano, F.; Poli, D.; Squarcialupi, L.; Betti, M.; Trincavelli, L.; Martini, C.; Dal Ben, D.; Thomas, A.; Volpini, R.; Colotta, V. *Bioorganic Med. Chem.* **2015**, *23*, 9–21. https://doi.org/10.1016/j.bmc.2014.11.033
13. Martínez, A.; Gutiérrez-de-Terán, H.; Brea, J.; Raviña, E.; Loza, M. I.; Cadavid, M. I.; Sanz, F.; Vidal, B.; Segarra, V.; Sotelo, E. *Bioorganic Med. Chem.* **2008**, *16*, 2103–2113. https://doi.org/10.1016/j.bmc.2007.10.103

14. Vorob'ev, A. Y. *Chem. Heterocycl. Compd.* **2019**, *55*, 695–697. https://doi.org/10.1007/s10593-019-02522-5
15. Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1957**, 4506. https://doi.org/10.1039/jr9570004506
16. Zheng, Z.; Ma, S.; Tang, L.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2014**, *79*, 4687–4693. https://doi.org/10.1021/jo500298j
17. Song, L.; Tian, X.; Lv, Z.; Li, E.; Wu, J.; Liu, Y.; Yu, W.; Chang, J. *J. Org. Chem.* **2015**, *80*, 7219–7225. https://doi.org/10.1021/acs.joc.5b01183
18. Bhatt, A.; Singh, R. K.; Sarma, B. K.; Kant, R. *Tetrahedron Lett.* **2019**, *60*, 151026. https://doi.org/10.1016/j.tetlet.2019.151026
19. Bhatt, A.; Singh, R. K.; Kant, R.; Sarma, B. K. *Synthesis.* **2019**, *51*, 3883–3890. https://doi.org/10.1055/s-0037-1611906
20. Li, Y.; Ye, Z.; Chen, N.; Chen, Z.; Zhang, F. *Green Chem.* **2019**, *21*, 4035–4039. https://doi.org/10.1039/C9GC01895F
21. Bartels, B.; Bolas, C. G.; Cueni, P.; Fantasia, S.; Gaeng, N.; Trita, A. S. *J. Org. Chem.* **2015**, *80*, 1249–1257. https://doi.org/10.1021/jo502536t
22. Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080–15081. https://doi.org/10.1021/ja905056z
23. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis.* **1977**, 1-17. https://doi.org/10.1055/s-1977-24260
24. Hajós, G.; Timári, G.; Messmer, A.; Zagyva, A.; Miskolczi, I.; Schantl, J. G. A New Synthesis of Thes-Triazolo[1,5-a]Pyridine Ring System. *Monatsh. Chem.* **1995**, *126*, 1213–1215. https://doi.org/10.1007/BF00824299
25. Filák, L.; Riedl, Z.; Egyed, O.; Czugler, M.; Hoang, C. N.; Schantl, J. G.; Hajós, G. *Tetrahedron* **2008**, *64*, 1101–1113. https://doi.org/10.1016/j.tet.2007.10.103
26. Okamoto, T.; Hirobe, M.; Tamai, Y.; Yabe, E. *Chem. Pharm. Bull.* **1966**, *14*, 506–512. https://doi.org/10.1248/cpb.14.506
27. Yamashita, Y.; Hayashi, T.; Masumura, M. *Tetrahedron Lett.* **1984**, *25*, 4429–4432. https://doi.org/10.1016/S0040-4039(01)81457-X
28. Vorob'ev, A. Y.; Supranovich, V. I.; Borodkin, G. I.; Shubin, V. G. *Beilstein J. Org. Chem.* **2017**, *13*, 800–805. https://doi.org/10.3762/bjoc.13.80
29. Luo, Y.; Hu, Y. *Arch. Pharm.* **2006**, *339*, 262–266. https://doi.org/10.1002/ardp.200500227
30. Tao, X.; Hu, Y. *Med. Chem.* **2010**, *6*, 65–69. https://doi.org/10.2174/157340610791321505

31. Abramov, P. A.; Brylev, K. A.; Vorob'ev, A. Y.; Gatilov, Y. V.; Borodkin, G. I.; Kitamura, N.; Sokolov, M. N. *Polyhedron* **2017**, *137*, 231–237. https://doi.org/10.1016/j.poly.2017.08.046
32. Tsuchiya, T.; Kurita, J.; Snieckus, V. *J. Org. Chem.* **1977**, *42*, 1856–1862. https://doi.org/10.1021/jo00431a007
33. Huisgen, R.; Grashey, R.; Krischke, R. *Justus Liebigs Ann. Chem.* **1977**, *1977*, 506–527. https://doi.org/10.1002/jlac.197719770316
34. Supranovich, V. I.; Vorob'ev, A. Y.; Borodkin, G. I.; Gatilov, Y. V.; Shubin, V. G. *Tetrahedron Lett.* **2016**, *57*, 1093–1096. https://doi.org/10.1016/j.tetlet.2016.01.092
35. Supranovich, V. I.; Borodkin, G. I.; Vorob'ev, A. Y.; Shubin, V. G. *Tetrahedron Lett.* **2014**, *55*, 5377–5380. https://doi.org/10.1016/J.TETLET.2014.08.015