UDC 547.854.856

N.V. Smetanin, S.A. Varenichenko, A.V. Kharchenko, O.K. Farat, V.I. Markov

SYNTHESIS OF NEW SUBSTITUTED PYRIDINES VIA VILSMEIER-HAACK REAGENT

Ukrainian State University of Chemical Technology, Dnipro, Ukraine

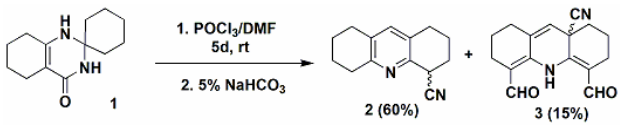
New substituted pyridines were synthesized by the reaction of spiroimidazolidinones with the Vilsmeier-Haack reagent (PBr_3/DMF) with satisfactory yields. The reaction proceeds as an electrophilic trigger process according to the push-pull mechanism due to the anomeric effect of two nitrogen atoms with an increase in the primary heterocycle. An explanation is proposed for the different chemical behavior of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one and spiroimidazolidinones under Vilsmeier-Haack reaction conditions. The likely reason is the hybridization of the amine (enamine) nitrogen atom in the structure of heterocycles. The reaction of spiroimidazolidinones with the Vilsmeier-Haack reagent results in formylation of the ammine nitrogen atom with subsequent reaction steps; and in the case of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one, the reaction results in formylation of carbon atom followed by heterocycle opening and its intramolecular cyclization. The synthesized new pyridine derivatives, due to the presence of several reaction centers in them, are of interest not only as potential pharmacologically active compounds, but also as low-molecular building blocks for organic synthesis.

Keywords: substituted pyridine, Vilsmeier-Haack reagent, trigger process, rearrangement, spiroimidazolidinone.

DOI: 10.32434/0321-4095-2023-146-1-34-39

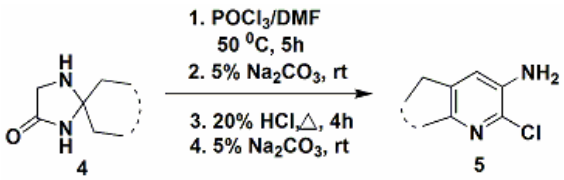
Introduction

Previously, we discovered the rearrangement of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one 1 into substituted hydroacridines 2 and 3 under the action of the Vilsmeier-Haack reagent [1] (Scheme 1).



Scheme 1

The discovery of this reaction served as a powerful impetus for the study of similar reactions on other model compounds containing heterocycles with geminally located heteroatoms, for example, see the work [2]. In the study [3], we described the rearrangement of spiroimidazolidinones to fused pyridines 5 (Scheme 2). Based on the rearrangement products, a number of new useful derivatives were synthesized [4–6]. Many articles [7–13] have been devoted to the synthesis of the pyridine ring, and works in recent years (for example, see refs. [14,15]) confirmed the importance of this class of compounds.



Scheme 2

Annulated pyridines 5 are functional compounds that can be used not only as potential biologically active compounds, but also as low molecular weight building blocks for organic synthesis.

Results and discussion

In light of the above, it was of interest to introduce another halogen into the molecules of substituted pyridines. Of all the phosphorus halides,

phosphorus tribromide is the most accessible, so it was decided to use it as the Lewis acid in the Vilsmeier-Haack reagent for a similar rearrangement. As expected, annulated pyridines 10–13 were synthesized with satisfactory yields when the modified Vilsmeier–Haack reagent (PBr_3/DMF) reacted with compounds 6–9 (Scheme 3).

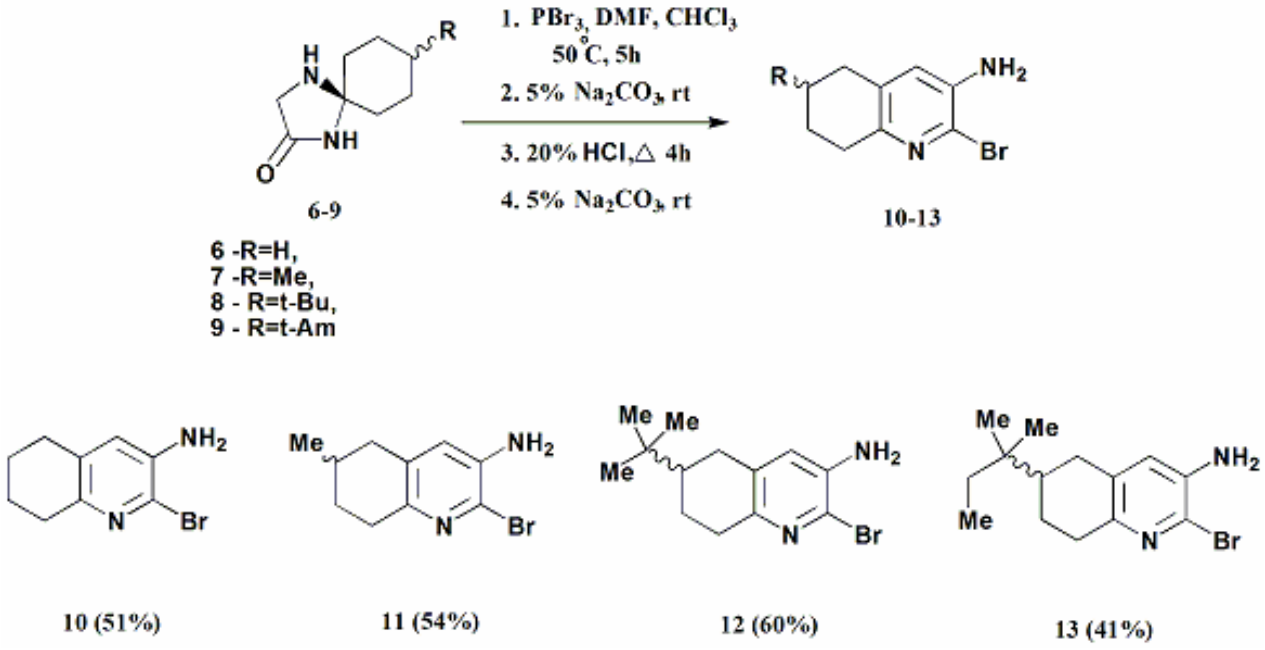
The structure of compounds 10–13 was confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

The most significant difference in the structures of compounds 1 and 6 for the course of rearrangements under the action of the Vilsmeier-Haack reagent is the hybridization of the amine nitrogen atom. In compound 6, this atom is in the sp^3-hybridized state, while it is in the sp^2-hybridized state in compound 1. It is the hybridization of the amine nitrogen atom that fundamentally changes the direction of recycling. In the case of compound 6 and its analogues 7–9, the lone electron pair of the amine nitrogen atom is in an sp^3-hybrid orbital, which is higher in energy than the unhybridized p-orbital of the enamine nitrogen atom, which is conjugated to the double bond and the carbonyl group in compound 1. This leads to the fact that in compounds 6–9, after the formation of the imidoyl chloride salt, the amine nitrogen atom is formylated, and in the case of compound 1, the carbon atom is formylated. The yields of annulated chloro- and bromopyridines upon interaction of the corresponding spiroimidazolidinones with $POCl_3$ or PBr_3 in DMF are very close [3], therefore the same conditions were chosen for the comparison of compounds 1 and 6, namely $POCl_3$ as a Lewis acid for the Vilsmeier-Haack complex (Scheme 4).

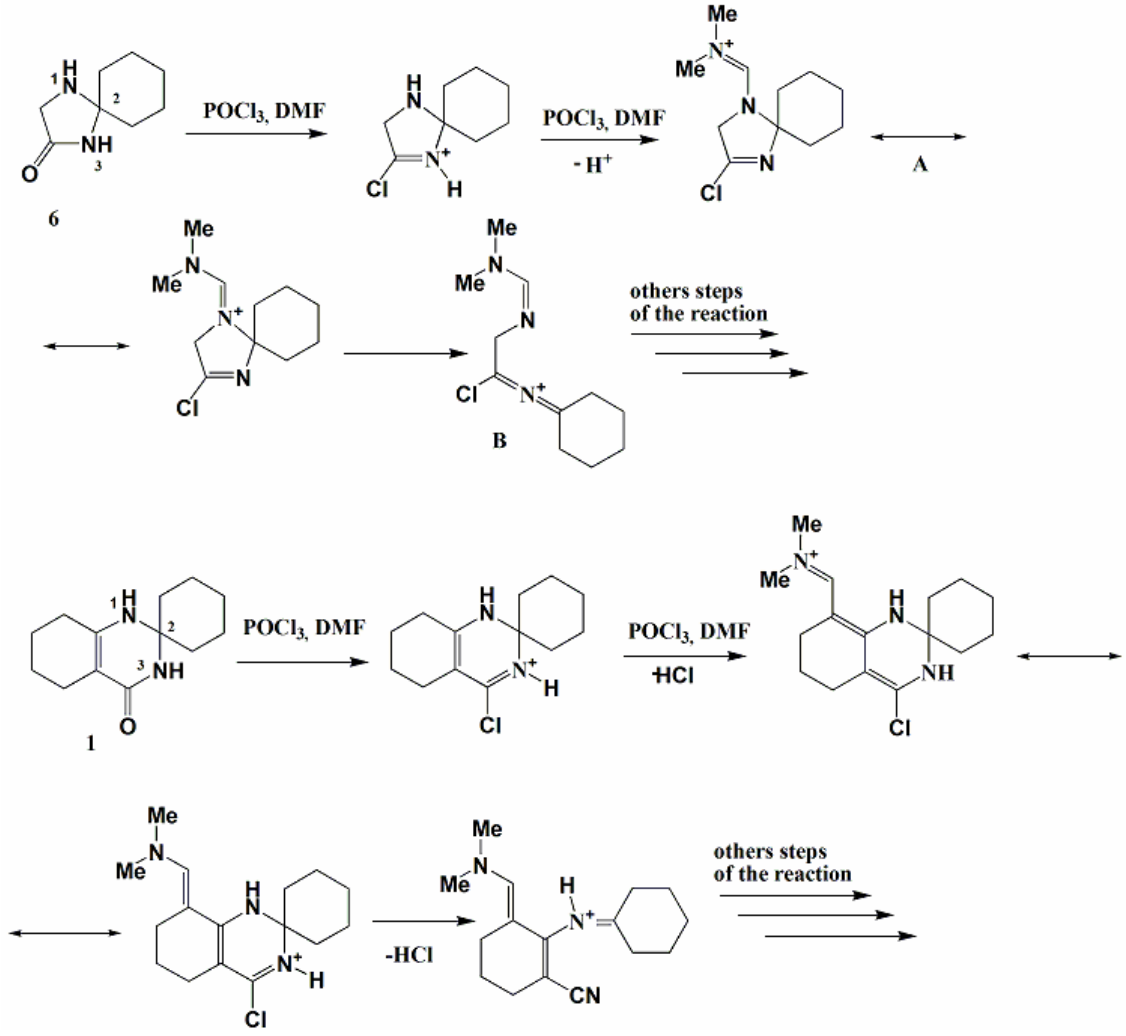
Formylation of the nitrogen atom in compounds 6–9 leads to the destruction of the N1–C2 bond, while in compound 1, the N3–C2 bond is broken. In all these conversion schemes, the push-pull mechanism is implemented. In the case of compounds 6–9, the electron-withdrawing atom is nitrogen N1, and the electron-donating atom is N3, while in the case of compound 1, it is the other way around. For compound 1, there are known examples of electrophilic rearrangement with breaking of the N1–C2 bond under the action of Brønsted protonic acids [16,17].

Conclusions

Thus, the number of examples of recyclization of 1,4-diazaspiro[4.5]decan-2-one derivatives under the action of the Vilsmeyer-Haack reagent (PBr_3/DMF) to form functionalized ringed pyridines has been expanded. The reaction takes place as an electrophilic rearrangement according to the push-pull mechanism, which is implemented due to the anomeric effect of the heteroatoms of the geminal N–C–N system, with an increase in the size of the primary heterocycle. An explanation of the differences between the reactions of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one and spiroimidazolidinones and their analogues is also offered under the influence of the Vilsmeier-Haack reagent.



Scheme 3



Scheme 4

Experimental

The ^{1}H NMR spectra were obtained by using a BrukerAvance II 400 instrument (400.13 MHz) in $CDCl_3$ and DMSO-d_6 using residual solvent peak as a reference. The mass spectra were recorded by means of a MX1321 instrument with direct injection of the sample at an ionization chamber temperature of 200^{0}C and with 70 eV ionizing electrons. Elemental analysis was performed by means of a LECO CHN-900 instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–i-PrOH as eluent. Melting points were carried out using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected.

2-Bromo-5,6,7,8-tetrahydroquinoline-3-amine (10)

When cooled with ice to 2.1 ml of DMF (27 mmol) was added 1.3 ml of PBr_3 (13.5 mmol). The resulting Vilsmeier-Haack reagent was dissolved in 15 ml of chloroform and 0.7 g (4.5 mmol) of compound 6 was added to the resulting reagent. The reaction mixture was heated with stirring at 50^{0}C for 4 h. Then the reaction mixture was cooled to 10^{0}C and neutralized with 5% aq. Na_2CO_3 solution (10 ml). A viscous oil was separated and dissolved in 10 ml of a 20% acetic acid solution. The reaction mixture was heated on a water bath at 50^{0}C with stirring for 4 h. After cooling to room temperature, the mixture was poured into water and neutralized with Na_2CO_3 solution. The precipitated solid compound 10 was filtered off and crystallized from methanol. Light yellow powder, mp: 94–95^{0}C, yield 51%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.70–1.84 (4H m, $2CH_2$), 2.62–2.75 (4H, m, $2CH_2$), 3.80 (2H, br.s., NH_2), 6.71 (1H, s, H–Ar). MS (FAB), *m/z* (I_{rel}, %): 228 $[M(Br^{81})]^+$ (100), 226 $[M(Br^{79})]^+$ (100). Calculated $C_9H_{11}BrN_2$: C 47.60; H 4.88; N 12.34. Found: C 47.74; H 4.99; N 12.21.

The procedure for the synthesis of compounds 11–13 is similar to the procedure for compound 10.

2-Bromo-6-methyl-5,6,7,8-tetrahydroquinolin-3-amine (11)

Light yellow powder, mp: 89–91^{0}C, yield 54%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.02 (3H, d, ^3J=6.4, CH_3), 1.39–1.49 (2H, m, CH_2), 1.81–1.92 (2H, m, CH_2), 2.24–2.31 (3H, m, CH_2, CH), 3.87 (2H, br.s., NH_2), 6.70 (1H, s, H–Ar). MS (EI), *m/z* (I_{rel}, %): 242 $[M(Br^{81})]^+$ (100), 240 $[M(Br^{79})]^+$ (100). Calculated $C_{10}H_{13}BrN_2$: C 49.81; H 5.43; N 11.62. Found: C 49.72; H 5.61; N 11.73.

6-tert-Butyl-2-bromo-5,6,7,8-tetrahydroquinoline-3-amine (12)

Light yellow powder, mp: 110–112^{0}C, yield 60%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 0.91 (9H, s, $3CH_3$), 1.41–1.46 (2H, m, CH_2), 2.01–2.07 (4H, m, $2CH_2$), 2.35–2.37 (1H, m, CH), 3.43 (2H, br.s., NH_2), 6.99 (1H, s, H–Ar). MS (EI), *m/z* (I_{rel}, %): 284 $[M(Br^{81})]^+$ (30), 282 $[M(Br^{79})]^+$ (30). Calculated $C_{13}H_{19}BrN_2$: C 55.13; H 6.76; N 9.89. Found: C 55.29; H 6.89; N 9.60.

2-Bromo-6-(1,1-dimethylpropyl)-5,6,7,8-tetrahydroquinolin-3-amine (13)

Light yellow powder, mp: 86–88^{0}C, yield 41%. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 0.81 (3H, t, ^3J=7.2, CH_3), 0.87 (6H, s, $2CH_3$), 1.34–1.45 (3H, m, CH_2, CH), 1.71–2.08 (6H, m, $3CH_2$), 4.57 (2H, br.s., NH_2), 7.86 (1H, s, H–Ar). MS (EI), *m/z* (I_{rel}, %): 298 $[M(Br^{81})]^+$ (30), 296 $[M(Br^{79})]^+$ (30). Calculated $C_{14}H_{21}BrN_2$: C 56.57; H 7.12; N 9.42. Found: C 56.79; H 7.29; N 9.20.

Acknowledgments

The work was carried out thanks to the named scholarship of the Verkhovna Rada of Ukraine for young scientists–doctors of sciences for 2022.

REFERENCES

1. *Rearrangement* of 5',6',7',8'-tetrahydro-1'H-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during Vilsmeier reaction / Markov V.I., Farat O.K., Varenichenko S.A., Velikaya E.V. // Mendeleev Commun. – 2012. – Vol.22. – P.101-102.

2. *Novel* rearrangement of 1,3-benzo(naphtho)dioxin-4(1)-ones under Vilsmeier-Haack reagent / Farat O.K., Kovtun A.V., Varenichenko S.A., Mazepa A.V., Markov V.I. // Monatsh. Chem. – 2021. – Vol.152. – P.95-101.

3. *Novel* rearrangement of substituted spiroimidazolidinones into quinoline derivatives via Vilsmeier-Haack reagent / Farat O.K., Smetanin N.V., Varenichenko S.A., Kaidash M.B., Zaliznaya E.V., Markov V.I. // Tetrahedron Lett. – 2021. – Vol.85. – Art. No. 153464.

4. *Reactions* of octahydroacridine-4-carbonitrile (carboxamide) with electrophilic reagents / Zaliznaya E.V., Farat O.K., Gorobets N.Yu., Markov V.I., Zubatyuk R.I., Mazepa A.V., Vashchenko E.V. // Chem. Heterocycl. Compd. – 2015. – Vol.51. – P.327-333.

5. *Functionalization* of tetra- and octahydroacridine derivatives through Michael addition / Zaliznaya E.V., Farat O.K., Varenichenko S.A., Mazepa A.V., Markov V.I. // Tetrahedron Lett. – 2016. – Vol.57. – No. 31. – P.3485-3487.

6. *Synthesis* and spectral properties of new xanthene chromophores / Farat O.K., Farat S.A., Tatarets A.L., Mazepa A.V., Markov V.I. // J. Mol. Struct. – 2019. – Vol.1176. – P.567-575.

7. *De novo* synthesis of 1,4-dihydropyridines and pyridines / Gati W., Rammah M.M., Rammah M.B., Couty F., Evano G. // J. Am. Chem. Soc. – 2012. – Vol.134. – No. 22. – P.9078-9081.

8. *Stout D.M., Meyers A.I.* Recent advances in the chemistry of dihydropyridines // Chem. Rev. – 1982. – Vol.82. – No. 2. – P.223-243.

9. *Pyridine* and pyrimidine derivatives as privileged scaffolds in biologically active agents / Chiacchio A.M., Iannazzo D., Romeo R., Giofre V.S., Legnani L. // Curr. Med. Chem. – 2019. – Vol.26. – No. 40. – P.7166-7195.

10. *Hill M.D.* Recent strategies for the synthesis of pyridine derivatives // Chem. A Eur. J. – 2010. – Vol.16. – No. 40. – P.12052-12062.

11. *Synthesis* of pyridine and dihydropyridine derivatives by regio- and stereoselective addition to N-activated pyridines / Bull J.A., Mousseau J.J., Pelletier G., Charette A.B. // Chem. Rev. –2012. – Vol.112. – No. 5. – P.2642-2713.

12. *Spirocyclic* thienopyrimidines: synthesis, new rearrangement under Vilsmeier conditions and in silico prediction of anticancer activity / Kovtun A.V., Tokarieva S.V., Varenichenko S.A., Farat O.K., Mazepa A.V., Dotsenko V.V., Markov V.I. // Biopolym. Cell. – 2020. – Vol.36. – No. 4. – P.279-293.

13. *Kasyan A., Wagner C., Maier M.E.*, Regiochemistry of the reductive Heck coupling of 2-azabicyclo[2.2.1]hept-5-ene. Synthesis of epibatidine analogues // Tetrahedron. – 1998. – Vol.54. – No. 28. – P.8047-8054.

14. *Borane-catalyzed* C3-alkylation of pyridines with imines, aldehydes, or ketones as electrophiles / Liu Z., He J.H., Zhang M., Shi Z.J., Tang H., Zhou X.Y., et al. // J. Am. Chem. Soc. – 2022. – Vol.144. – P.4810-4818.

15. *C3-Selective* trifluoromethylthiolation and difluoromethylation of pyridines and pyridine drugs via dihydropyridine intermediates / Zhou X.Y., Zhang M., Liu Z., He J.H., Wang X.C. // J. Am. Chem. Soc. – 2022. – Vol.144. – No. 32. – P.14463-14470.

16. *Zigeuner G., Gubitz G.* Uber das Tetrahydrospiro[cyclohexan-1,2'(1'*H*)-chinazolin]-4'(3'*H*)-on // Monatsh. Chem. – 1970. – B.101. – S.1547-1558.

17. *Upadysheva A.V., Grigor'eva N.D., Znamenskay A.P.* Intramolecular rearrangement of two-ring 2,2-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidines under the influence of polyphosphoric acid // Chem. Heterocycl. Compd. – 1977. – Vol.13. – P.11240-1243.

Received 14.08.2022

СИНТЕЗ НОВИХ ЗАМІЩЕНИХ ПІРИДИНІВ ЗА ДОПОМОГОЮ РЕАКТИВУ ВІЛЬСМАЙЕРА-ХААКА

М.В. Сметанін, С.А. Вареничeнко, О.В. Харченко, О.К. Фарат, В.І. Марков

Нові заміщені піридини були одержані реакцією спіроімідазолідинонів з реактивом Вільсмаєра-Хаака (PBr_3/DMF) із задовільними виходами. Реакція протікає як електрофільний тригерний процес за механізмом push-pull за рахунок аномерного ефекту двох атомів азоту зі збільшенням розміру первинного гетероциклу. Пропонується пояснення різної хімічної поведінки 5',6',7',8'-тетрагідро-1'H-спіро[циклогексан-1,2'-хіназолін]-4'(3'H)-ону та спіроімідазолідинонів в умовах реакції Вільсмайєра-Хаака. Ймовірною причиною є гібридизація амінного (енамінного) атома азоту в структурі гетероциклів. Реакція спіроімідазолідинонів з реактивом Вільсмаєра-Хаака приводить до формілювання атома азоту аміна з наступними стадіями реакції, а у випадку 5',6',7',8'-тетрагідро-1'H-спіро[циклогексан- 1,2'-хіназолін]-4'(3'H)-он – формілювання атома вуглецю з подальшим розкриттям гетероциклу та його внутрішньомолекулярною циклізацією. Одержані нові похідні піридину завдяки наявності в них кількох реакційних центрів становлять інтерес не лише як потенційні фармакологічно активні сполуки, а й як низькомолекулярні будівельні блоки для органічного синтезу.

Ключові слова: заміщений піридин, реагент Вільсмайєра-Хаака, тригерний процес, перегрупування, спіроімідазолідинон.

SYNTHESIS OF NEW SUBSTITUTED PYRIDINES VIA VILSMEIER-HAACK REAGENT

N.V. Smetanin, S.A. Varenichenko*, A.V. Kharchenko, O.K. Farat, V.I. Markov

Ukrainian State University of Chemical Technology, Dnipro, Ukraine

***e-mail: svetlanavarenichenko@gmail.com**

New substituted pyridines were synthesized by the reaction of spiroimidazolidinones with the Vilsmeier-Haack reagent (PBr_3/DMF) with satisfactory yields. The reaction proceeds as an electrophilic trigger process according to the push-pull mechanism due to the anomeric effect of two nitrogen atoms with an increase in the primary heterocycle. An explanation is proposed for the different chemical behavior of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one and spiroimidazolidinones under Vilsmeier-Haack reaction conditions. The likely reason is the hybridization of the amine (enamine) nitrogen atom in the structure of heterocycles. The reaction of spiroimidazolidinones with the Vilsmeier-Haack reagent results in formylation of the ammine nitrogen atom with subsequent reaction steps; and in the case of 5',6',7',8'-tetrahydro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one, the reaction results in formylation of carbon atom followed by heterocycle opening and its intramolecular cyclization. The synthesized new pyridine derivatives, due to the presence of several reaction centers in them, are of interest not only as potential pharmacologically active compounds, but also as low-molecular building blocks for organic synthesis.

Keywords: substituted pyridine; Vilsmeier-Haack reagent; trigger process; rearrangement; spiroimidazolidinone.

REFERENCES

1. Markov VI, Farat OK, Varenichenko SA, Velikaya EV. Rearrangement of 5',6',7',8'-tetrahydro-1'H-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during Vilsmeier reaction. *Mendeleev Commun*. 2012; 22: 101-102. doi: 10.1016/j.mencom.2012.03.017.

2. Farat OK, Kovtun AV, Varenichenko SA, Mazepa AV, Markov VI. Novel rearrangement of 1,3-benzo(naphtho)dioxin-4(1)-ones under Vilsmeier Haack reagent. *Monatsh Chem*. 2021; 152: 95-101. doi: 10.1007/s00706-020-02733-z.

3. Farat OK, Smetanin NV, Varenichenko SA, Kaidash MB, Zaliznaya EV, Markov VI. Novel rearrangement of substituted spiroimidazolidinones into quinoline derivatives via Vilsmeier-Haack reagent. *Tetrahedron Lett*. 2021; 85: 153464. doi: 10.1016/j.tetlet.2021.153464.

4. Zaliznaya EV, Farat OK, Gorobets NYu, Markov VI, Zubatyuk RI, Mazepa AV, et al. Reactions of octahydroacridine-4-carbonitrile (carboxamide) with electrophilic reagents. *Chem Heterocycl Compd*. 2015; 51: 327-333. doi: 10.1007/s10593-015-1703-8.

5. Zaliznaya EV, Farat OK, Varenichenko SA, Mazepa AV, Markov VI. Functionalization of tetra- and octahydroacridine derivatives through Michael addition. *Tetrahedron Lett*. 2016; 57: 3485-3487. doi: 10.1016/j.tetlet.2016.06.096.

6. Farat OK, Farat SA, Tatarets AL, Mazepa AV, Markov VI. Synthesis and spectral properties of new xanthene chromophores. *J Mol Struct*. 2019; 1176: 567-575. doi: 10.1016/j.molstruc.2018.09.002.

7. Gati W, Rammah MM, Rammah MB, Couty F, Evano G. De novo synthesis of 1,4-dihydropyridines and pyridines. *J Am Chem Soc*. 2012; 134: 9078-9081. doi: 10.1021/ja303002a.

8. Stout DM, Meyers AI. Recent advances in the chemistry of dihydropyridines. *Chem Rev*. 1982; 82: 223-243. doi: 10.1021/cr00048a004.

9. Chiacchio MA, Iannazzo D, Romeo R, Giofre SV, Legnani L. Pyridine and pyrimidine derivatives as privileged scaffolds in biologically active agents. *Curr Med Chem*. 2019; 26: 7166-7195. doi: 10.2174/0929867325666180904125400.

10. Hill MD. Recent strategies for the synthesis of pyridine derivatives. *Chem A Eur J*. 2010; 16: 12052-12062. doi: 10.1002/chem.201001100.

11. Bull JA, Mousseau JJ, Pelletier G., Charette AB. Synthesis of pyridine and dihydropyridine derivatives by regio- and stereoselective addition to N-activated pyridines. *Chem Rev*.

2012; 112: 2642-2713. doi: 10.1021/cr200251d.

12. Kovtun AV, Tokarieva SV, Varenichenko SA, Farat OK, Mazepa AV, Dotsenko VV, et al. Spirocyclic thienopyrimidines: synthesis, new rearrangement under Vilsmeier conditions and in silico prediction of anticancer activity. *Biopolym Cell*. 2020; 36(4): 279-293. doi: 10.7124/bc.000A2C.

13. Kasyan A, Wagner C, Maier ME. Regiochemistry of the reductive Heck coupling of 2-azabicyclo[2.2.1]hept-5-ene. Synthesis of epibatidine analogues. *Tetrahedron*. 1998; 54: 8047-8054. doi: 10.1016/S0040-4020(98)00443-8.

14. Liu Z, He JH, Zhang M, Shi ZJ, Tang H, Zhou XY, et al. Borane-catalyzed C3-alkylation of pyridines with imines, aldehydes, or ketones as electrophiles. *J Am Chem Soc*. 2022; 144: 4810-4818. doi: 10.1021/jacs.2c00962.

15. Zhou XY, Zhang M, Liu Z, He JH, Wang XC. C3-selective trifluoromethylthiolation and difluoromethylation of pyridines and pyridine drugs via dihydropyridine intermediates. *J Am Chem Soc*. 2022; 144: 14463-14470. doi: 10.1021/jacs.2c06776.

16. Zigeuner G, Gubitz G. Uber das Tetrahydrospiro[cyclohexan-1,2'(1'H)-chinazolin]-4'(3'H)-on. *Monatsh Chem*. 1970; 101: 1547-1558. (*in German*). doi: 10.1007/BF00911421.

17. Upadysheva AV, Grigor'eva ND, Znamenskay AP. Intramolecular rearrangement of two-ring 2,2-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidines under the influence of polyphosphoric acid. *Chem Heterocycl Compd*. 1977; 13: 11240-1243. doi: 10.1007/BF00475956.