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NOVEL EXAMPLES OF ELECTROPHILIC REARRANGEMENT OF SUBSTITUTED PYRIMIDIN-4-ONES UNDER VILSMEIER-HAACK REACTION CONDITION

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The critical influence of the size of aliphatic annulated cycles in 2,2-disubstituted pyrimidin-4-ones on the conditions of rearrangement under the action of Vilsmeier-Haack reagent was established. Compounds with a 5-membered ring cycle to pyrimidin-4-one require heating at 110°C for 2 h due to the coplanar arrangement of dimethyliminium and chloriminium groups in intermediates, which leads to placement of a positive charge on the nitrogen atom of the dimethylamino group, which is unfavorable for the reaction. In the case of 6- and 7-membered annulated cycles, there is interatomic repulsion in the intermediates from the hydrogen atoms of methyl and methylene groups, as well as hydrogen atoms of CH and NH, which contributes to placement of a positive charge on the endocyclic atom of nitrogen and chloriminium salt and easier rearrangement. The size of aliphatic annealed and spirocycles to the pyrimidine framework affects not only the reaction conditions but also the formation of products.

Keywords: pyrimidin-4-one, substituted pyridine, Vilsmeier-Haack reagent, rearrangement, X-ray diffraction study.

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Introduction

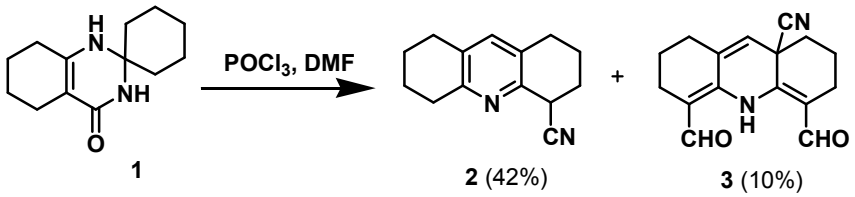
Previously, we discovered an unprecedented rearrangement of 5',6',7',8'-tetrahydro-1"H-spiro[cyclohexane-1,2'-quinazoline]-4'(3"H)-one 1 under the action of the Vilsmeier-Haack reagent to form a mixture of hydroacridine derivatives 2 and 3 [1] (Scheme 1). This reaction was further examined in ref. [2], where similar transformations with related compounds were considered. Other electrophilic rearrangements for similar compounds were considered elsewhere [3–7].

No less interesting was the reaction of 1,3-benz(naphth)oxazines with the Vilsmeier-Haack reagent, leading to the preparation of previously unknown functionalized xanthene derivatives [8,9]. Based on these aldehydes, promising fluorophores and dyes have been synthesized [10,11].

Results and discussion

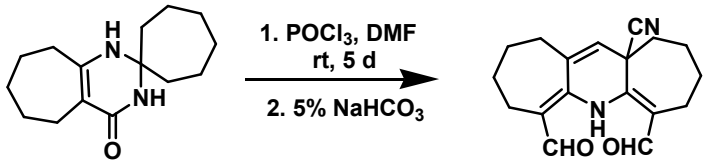
Further work was continued on the study of the effect of the sizes of saturated rings in pyrimidone derivatives 1 during formylation under the conditions of the Vilsmeier-Haack reaction. A similar rearrangement with a spirocompound 4 with the excess of Vilsmeier-Haack reagent leads to the formation of diformyl derivative 5 with moderate yield (Scheme 2).

The structure of compound 5 was determined by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Additionally, X-ray diffraction study was performed (Figure). In the ^{1}H NMR spectrum



1 **2** (42%) **3** (10%)

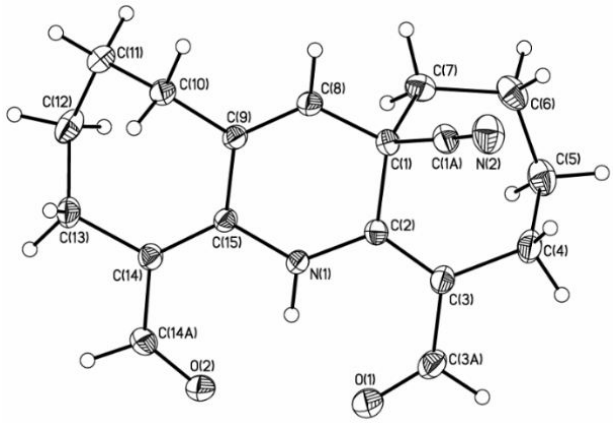
Scheme 1



4 5 (55%)

Scheme 2

recorded in $CDCl_3$, the signal of the NH hydrogen atom in the form of a singlet resonates at 14.40 ppm, and the signals of hydrogen atoms of formyl groups have chemical shifts of 9.81 and 9.43 ppm. The peak of the alkene hydrogen atom of CH is observed at 5.73 ppm, and aliphatic hydrogen atoms are manifested in a strong field in the form of a multiplet. In the ^{13}C NMR spectrum, the signals of the formyl groups have chemical shifts of 191.3 and 191.0 ppm, and the signal of the nitrile group was at 118.3 ppm. The mass spectrum of this compound with electron ionization is characterized by the presence of a peak of molecular ions with m/z 296 $[M]^+$ (41%) relative to the main peak with m/z 278 $[M-H_2O]^+$ (100%).

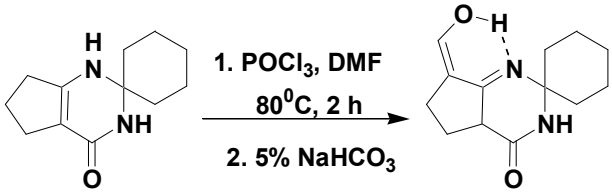


The structure of compound 5 according to X-ray diffraction study. Thermal ellipsoids of non-hydrogen atoms are represented at a probability level of 50%

All three cycles in compound 5 are not flat. The hydropyridine cycle has the shape of a twisted boat. The deviation of C1 and C2 atoms from the C9=C8 double bond plane is 0.041 and 0.138, respectively. Aldehyde groups are almost coplanar C=C double bonds of cycloheptene cycles and have S-cis conformation relative to these double bonds (C2−C3−C3A−O1 and C15−C14−C14A−O2 torsion angles are $-0.2(2)^0$ and $-0.8\ (2)^0$, respectively). This conformation of acroleine fragments is stabilized by the formation of bifurcated intramolecular hydrogen bonds in which the NH hydrogen atom participates: H1···O1 1.962 Å, N−H···O 134.5^0, H1···O2 1.929 Å, N−H···O 135.5^0.

The example of the formation of compound 5 shows that an increase in the size of the aliphatic spiro- and annulus cycles per methylene group as compared with compound 1 leads to a similar rearrangement, but unlike the previous reaction of carbonitrile analog 2 was not detected.

The reaction of spiropyrimidine 6, in which the annulus cycle is reduced by one methylene group compared to compound 1, with an excess of Vilsmeier-Haack reagent at room temperature for a week or heating to 80^{0}C for 2 h does not lead to similar rearrangement, but only formylation product 7 (Scheme 3). The aldehyde group in compound 7 in DMSO solution exists as vinyl alcohol.



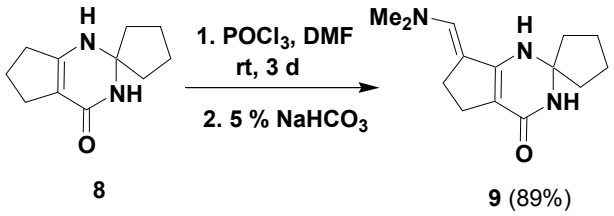
6 7 (66%)

Scheme 3

According to ^1H NMR spectrum data (in DMSO), the signals of OH and NH hydrogen atoms appear as extended singlets at 9.51 and 8.71 ppm, respectively; and the CHON hydrogen atom signal has a clear singlet signal at 8.45 ppm. It should be noted that compound 7 in DMSO is in the form of vinyl alcohol, due to the ability to form intramolecular hydrogen bonds. To form a stronger hydrogen bond, the conjugation between the amine and amide groups must be disrupted, which in this case is able to provide an unshared electron pair of the nitrogen atom to form a hydrogen bond. This change in the positions of the double bonds is evidenced by the appearance in the ^1H NMR spectrum of compound 7 of the methine atom signal of the C−4'hydrogen atom at 3.89 ppm in the form of a triplet with SSCC ^3J=9.3 Hz. If the aldehyde

group were not in the form of vinyl alcohol, the chemical shift of the NH hydrogen atom would be ≈11 ppm [2]. In the mass spectrum of this compound (FAB ionization) there is a peak of protonated molecules with m/z 235 $[M+H]^+$ (100%).

The reaction of compound 8 with Vilsmeier-Haack reagent at room temperature for 3 days also does not lead to rearrangement and the introduction of dimethylaminomethine group with the formation of compound 9 [2] (Scheme 4).



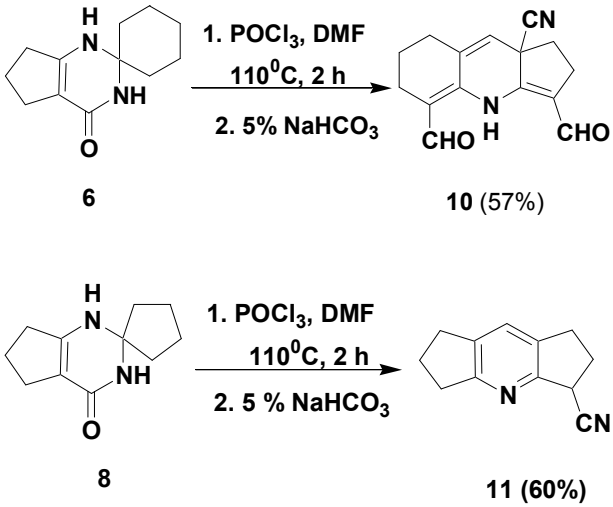
8 **9** (89%)

Scheme 4

From these examples, it is clear that the rearrangement of heminal azines does not occur in the case of 5-membered pyrimidone-annulled cycles, which is quite unexpected, since the differences, at first glance, should not be critical. In addition, in the case of the reaction of compound 4 with Vilsmeier-Haack reagent, no analogue of product 2 was isolated and the yield of diformyl derivative 5 was significantly higher than that of product 3. All data indicate that the size of aliphatic annulus and spirocycles is critical not only for reactions, but also for the formation of products.

In this regard, it was decided to raise the reaction temperature with Vilsmeier-Haack reagent to 110°C for compounds 6 and 8. As expected, rearrangement occurred under such conditions, but in the case of compound 8, substituted pyridine 11 is formed, and diformyl derivative 10 is produced in the case of compounds 6 (Scheme 5). Of course, the formation of only these products cannot be stated unequivocally, but only these products were identified, which are undoubtedly formed in larger quantities.

The structures of compounds 10 and 11 were determined by multinuclear NMR spectroscopy (on ^1H and ^{13}C nuclei) and mass spectrometry. In the ^1H NMR spectrum (in DMSO) of compound 11, there is a signal of an aromatic hydrogen atom at 7.30 ppm and a signal of the methine atom of CH in the form of a triplet at 4.30 ppm. According to ^1H NMR spectroscopy in DMSO for compound 10, signals of two formyl groups were observed at 9.61 and 9.60 ppm as well as a signal of a hydrogen atom of the NH group with a chemical shift of 12.26 ppm. The signal of the alkene hydrogen atom resonates at 6.33 ppm, and aliphatic hydrogen atoms appear in a strong field.



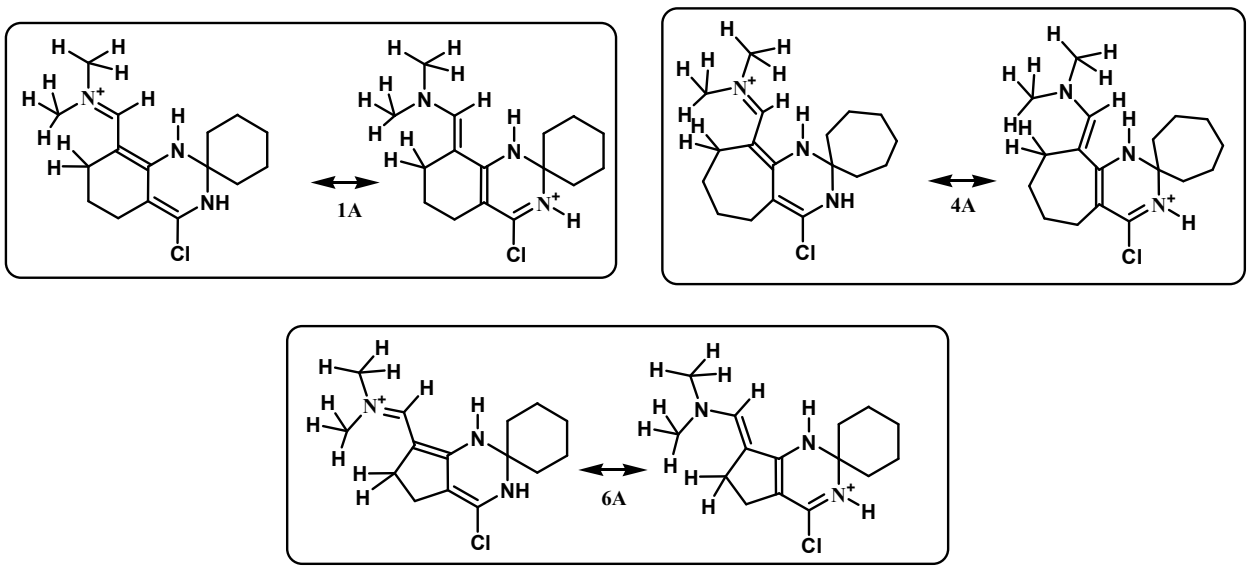
6 **10** (57%)

8 **11** (60%)

Scheme 5

To explain the reasons for such different behavior of spirocompounds 1, 4 and 6 in the formylation of Vilsmeier-Haack reagent, it is necessary to consider the structure of the primary intermediates of these reactions. Animidoyl chloride salt is formed in the first stage of the reaction, which, due to the deprotonation of the methylene group C–8, makes this position active for electrophile attack [1]. This is followed by a second attack with chloriminium salt at this position with the formation of the primary product of Vilsmeier-Haack. It is at this stage that differences in the reactivity of compounds 1, 4 and 6 begin (Scheme 6).

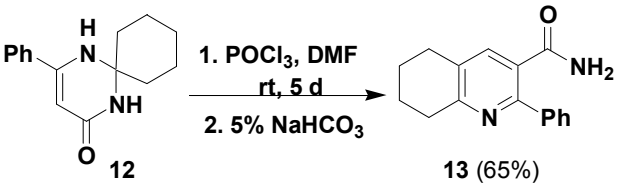
As mentioned earlier, compounds 1 and 4 are recycled under the action of Vilsmeier-Haack reagent at room temperature for 5 days, and compound 6 is only formylated under these conditions. For intermediates 1A, 4A and 6A, we can write boundary structures in which the positive charge is on the endocyclic nitrogen atom of the chloriminium group or on the nitrogen atom of the dimethylamino group. To facilitate the reaction, the positive charge should be on the nitrogen atom of the chloriminium group, because it is this nitrogen atom that is a part of the C–N bond, which is broken during the reaction. Obviously, the location of the positive charge on the nitrogen atom of the dimethyliminium group in these intermediates should be more advantageous, because it is further stabilized by the electron σ-bonds of the CH of the two methyl groups (superconjugation effect). Only the noncoplanarity of the chromophore system of the dimethyliminium group and the substituted pyrimidine can interfere with the efficient



Scheme 6

location of the positive charge on this atom. In the case of intermediates 1A and 4A, there is an interatomic repulsion between the hydrogen atoms of the methylene and methyl groups, which leads to the reversal of the dimethyliminium group relative to the substituted pyrimidine framework and the derivation of this group from the effective π-conjugation with the chloriminium group. That is, expressed in terms of conjugation, the contribution of the boundary structure with the location of the positive charge on the nitrogen atom of the chloriminium group for intermediates 1A and 4A is more significant. An additional reason for the disruption of the effective π-conjugation between the dimethyliminium and iminium groups is the interatomic repulsion between the hydrogen and CH atoms. In the case of intermediate 6A, a small 5-membered pyrimidine-annealed cycle does not cause serious spatial obstacles to the coplanar arrangement of the dimethyliminium and chloriminium groups, so placement of a positive charge on the nitrogen atom in the intermediate is more necessary, which is achieved by heating at 110°C.

Reaction of compound 12 with Vilsmeier-Haack reagent leads to the formation of the expected amide 13 (Scheme 7).



Scheme 7

The structure of compound 13 was proved by ^{1}H NMR and ^{13}C spectroscopy as well as mass spectrometry.

Conclusions

Thus, it was shown that the hydrogenated derivatives of substituted pyrimidines 1 and 4 when formylated with Vilsmeier-Haack reagent are rearranged into derivatives of bis-annulated pyridine at room temperature for 5 days, while spirane 6 under these conditions is only formylated. The reason for such different behavior of compounds 1, 4 and 6 under the Vilsmeier-Haack reaction is the size of the partially saturated pyrimidine-annulated cycle, which affects the activation energy of the electrophilic opening of the pyrimidine cycle due to interatomic repulsion between hydrogen atoms and hydrogen intermediates. In the case of 6- and 7-membered cycles, the reaction occurs at room temperature, as they have a significant above-mentioned interatomic repulsion, and for a 5-membered cycle, where there is no such interatomic repulsion, heating at 110°C is required for 2 h. The size of aliphatic annulus and spirocycles to the pyrimidine framework affects not only the reaction conditions but also the formation of products. Thus, spiro compound 1, formed by 6-membered annulus and spirocycles, under the action of Vilsmeier-Haack reagent is rearranged into a mixture of two derivatives of hydroacridine 2 and 3. At the same time, compound 4, formed by 7-membered annulus and spirocycles, under similar conditions is transformed only to diformyl derivative 5. Compound 8, formed by 5-membered annulus

and spirocycles, when heated at 110°C for 2 h is recycled to bis-annulus pyridine 11. The small size of aliphatic cycles (5 members) promotes rapid cyclization between the primary formulation product and the enamine moiety [1] to the pyridine cycle (entropy factor). Increasing the size of aliphatic cycles to 7 members prevents rapid analogous cyclization, which results in the formylation of the enamine moiety followed by cyclization and formylation to a diformyl-derived bis-annulated pyridine. In the case of 6-membered aliphatic cycles, the formation of a mixture of two products with a predominance of the product with an aromatic pyridine cycle is observed.

Experimental part

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (400.13 MHz and 100.62 MHz for ^{1}H and ^{13}C, respectively) or Bruker Avance 200 spectrometer (200.13 MHz) in DMSO-d_6 or $CDCl_3$ using residual solvent peak (δ 2.50 ppm and 7.26 ppm; 39.50 ppm and 77.16 ppm for ^{1}H and ^{13}C, respectively) as a reference. The EI mass spectra were recorded on Kratos MS 30 with direct injection of the sample to the ionization chamber at the temperature of 250°C with 70 Ev ionizing electrons. The FAB mass spectra were recorded on a VG7070 spectrometer. Desorption of the ions from the solution of the samples in meta-nitrobenzyl alcohol was realized with a beam of argon atoms with energy 8 keV. Elemental analysis was performed on a LECO CHN-900 instrument. Melting points were determined using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected. The control of reactions and the purity of the obtained compounds were monitored by TLC on Merck Silica gel 60 F-254 plates with 10:1, v/v $CHCl_3$/MeOH as eluent.Compounds 4, 8 and 12 were obtained according to ref. [12], and compound 6 was prepared according to ref. [13].

5,7-Diformyl-2,3,4,6,8,9,10,11-octahydrodicyclohepta[b,e]pyridine-11a(1H)-carbonitrile (5)

When cooled with ice, Vilsmeier-Haack reagent was prepared with 2.3 ml (0.03 mol) of DMF and 0.92 (0.01 mxol) ml of $POCl_3$. 2.48 g (0.01 mol) of compound 4 was added to the obtained reagent and left at room temperature for 5 days. The reaction mass is poured onto ice and neutralized with aqueous $NaHCO_3$ solution. The precipitate formed is crystallized from i-PrOH. Yield 1.63 g (55%), yellow powder, mp=172−174°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 14.40 (1H, s, NH); 9.81 (1H, s, CHO); 9.43 (1H, s, CHO); 5.73 (1H, s, CH); 2.63−2.65 (2H, m, CH_2); 2.54−2.56 (2H, m, CH_2); 2.07−2.19 (2H, m, CH_2); 1.94−1.96 (2H, m, CH_2); 1.75−1.80 (8H, m, $4CH_2$).^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 191.5; 191.2; 129.0; 40.2; 38.2; 32.1; 28.0; 26.9; 26.8; 25.7; 24.1; 23.9. Mass spectrum (EI), m/z (I_{rel}, %): 296 $[M]^+$ (45). Found, %: C 72.83; H 6.96; N 9.33. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

7'-(Hydroxymethylene)-4a',5',6',7'-tetrahydrospiro[cyclohexane-1,2'-cyclopenta[d]pyrimidin]-4'(3'H)-one(7)

When cooled with ice, Vilsmeier-Haack reagent was prepared with 2.3 ml (0.03 mol) of DMF and 0.92 (0.01 mol) ml of $POCl_3$. 2.06 g (0.01 mol) of compound 6 was added to the obtained reagent and heated to temperature 60−70°C during 2 h. The reaction mass is poured onto ice and neutralized with aqueous $NaHCO_3$ solution. The precipitate formed is crystallized from acetonitrile. Yield 66%, light browncompound, mp=235−237°C. ^{1}H NMRspectrum (400 MHz, DMSO-d_6), δ, ppm: 9.51 (1H, s, OH); 8.71 (1H, s, CHOH); 8.47 (1H, s, NH); 3.90 (1H, m, CH); 1.05−2.22 (10H, m, $5CH_2$); 1.11−1.51 (4H, m, $2CH_2$). Mass spectrum (FAB), m/z (I_{rel}, %): 235 $[M+H]^+$ (100). Found, %: C 68.53; H 7.16; N 11.63. $C_{14}H_{18}N_2O_2$. Calculated, %: C 68.27; H 7.37; N 11.37.

3,5-Diformyl-1,2,4,6,7,8-hexahydro-9aH-cyclopenta[b]quinoline-9a-carbonitrile (10)

When cooled with ice, Vilsmeier-Haack reagent was prepared with 2.3 ml (0.03 mol) of DMF and 0.92 (0.01 mol) ml of $POCl_3$. 0.01 mol of compound 6 was added to the obtained reagent and heated to temperature 110°C during 2 h. The reaction mass is poured onto ice and neutralized with aqueous $NaHCO_3$ solution. The precipitate formed is crystallized from acetonitrile. Yield 57%, light brown compound, mp=112−115°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 12.26 (1H, s, NH); 9.60 (1H, s, CHO); 9.61 (1H, s, CHO); 6.33 (1H, s, CH); 1.52−2.82 (12H, m, $6CH_2$). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 193.7; 187.6; 145.2; 139.5; 133.6; 132.4; 131.2; 124.1; 118.3; 35.9; 31.8; 29.0; 28.2; 22.6; 21.7. Mass spectrum (EI), m/z (I_{rel}, %): 254 $[M]^+$ (48). Found, %: C 70.64; H 5.76; N 11.33. $C_{15}H_{14}N_2O_2$. Calculated, %: C 70.85; H 5.55; N 11.02.

1,2,3,5,6,7-Hexahydrodicyclopenta[b,e]pyridine-3-carbonitrile (11)

It was obtained similarly to compound 7. Yield 60%, yellow powder, mp=65−67°C(aq. EtOH). ^{1}H NMR spectrum(400 MHz, DMSO-d_6), δ, ppm (Hz): 7.30 (1H, s, H Ar); 4.30 (1H, t, ^{3}J=7.2, CH); 2.85−2.97 (4H, m, $2CH_2$); 2.75−2.80 (2H, m, CH_2); 1.78−2.00 (4H, m, $2CH_2$). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 163.7; 151.3; 134.4; 133.3; 127.1;

118.1; 41.2; 35.5; 33.8; 27.8; 27.5; 23.0. Mass spectrum (EI), m/z (I_{rel}, %): 184 $[M]^+$ (30). Found, %: C 78.35; H 6.41; N 15.36. $C_{12}H_{12}N_2$. Calculated, %: C 78.23; H 6.57; N 15.21.

2-Phenyl-5,6,7,8-tetrahydroquinoline-3-carboxamide(13)

Compound 12 (2.42 g, 0.01 mol) was mixed with 1 ml of DMF and the resulting paste was added in portions to Vilsmeier-Haack reagent prepared from 9.22 ml of DMF and 5.58 ml (0.06 mol) of $POCl_3$ under ice-cooling followed by room temperature for 30 minutes. The reaction mixture is kept for 5 days at room temperature, then poured onto ice and neutralized with aqueous $NaHCO_3$ solution until slightly alkaline reaction and filter the precipitate. Yield 65%, white powder, mp=223−225^{0}C (EtOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ ppm: 7.95 (2H, m, Ph); 7.62 (1H, s, H-4); 7.53 (2H, br. s., NH_2); 7.47 (3H, m, Ph); 2.57−2.80 (4H, m, 5,8-CH_2); 1.64−1.83 (4H, m, 6,7-CH_2). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 171.3; 164.3; 155.3; 137.4; 134.1; 133.0; 131.2; 130.5; 128.5; 126.5; 32.2; 27.7; 22.1; 21.5. Mass spectrum (EI), m/z (I_{rel}, %): 252 $[M]^+$ (78). Found, %: C 76.38; H 6.48; N 11.17. $C_{16}H_{16}N_2O$. Calculated, %: C 76.16; H 6.39; N 11.10.

X-ray diffraction study

Crystals of 5 ($C_{18}H_{20}N_2O_2$, M_r=296.36) are triclinic, space group P−1, at 120 K: a=8.1133(5) Å, b=9.6013(6) Å, c=10.1121(6) Å, α=85.841(1)^0, β=88.144(1)^0, γ=71.878(1)^0, V=746.63(8) Å^3, Z=2, d_{calc}=1.318 g/cm^3: μ(MoK_α)=0.087 mm^{-1}, F(000)=316. Intensities of 11006 reflections were measured with a Bruker APEX 2 Duo diffractometer (CCD detector) [l(MoK_α) 0.71073 Å, w-scans, 2q<63^0) and 4911 independent reflections [R_{int}=0.0315] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The H(C) atom positions were calculated, these atoms were refined in the isotropic approximation within the riding model. For 5, the refinement converged to wR_2=0.1371 and GOF=0.979 for all independent reflections (R_1=0.0492 was calculated against F for 3310 observed reflections with I>2σ(I)). Crystal data were deposited at Cambridge Crystal Database, deposition number CCDC2156638. All crystallography calculations were performed using the SHELX software [14,15].

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НОВІ ПРИКЛАДИ ЕЛЕКТРОФІЛЬНОГО ПЕРЕГРУПУВАННЯ ЗАМІЩЕНИХ ПІРИМІДИН-4-ОНІВ В УМОВАХ РЕАКЦІЇ ВІЛЬСМАЙЄРА-ХААКА

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Встановлено критичний вплив розміру аліфатичних циклів анельованих до 2,2-дизаміщених піримідин-4-онів на умови перегрупування під дією реактиву Вільсмайєра-Хаака. Сполуки з анельованим 5-членним циклом до піримідин-4-ону потребують нагрівання протягом 2 год при 110^{0}C через копланарне розташування диметилімінієвої та хлорімінієвої груп в проміжних сполуках, що приводить до розташування позитивного заряду на атомі азоту диметиламіногрупи, що є несприятливим фактором для перебігу реакції. У випадку 6- і 7-членних анельованих циклів в проміжних сполуках відбувається міжатомне відштовхування між атомами водню метильної та метиленової груп, а також атомів водню CH і NH, що сприяє знаходженню позитивного заряду на ендоциклічному атомі азоту хлормінієвої солі, і, як наслідок, полегшує перегрупування. Розмір аліфатичних анельованих і спіроциклів до піримідинового каркаса впливає не тільки на умови реакції, а й на утворення продуктів.

Ключові слова: піримідин-4-он, заміщений піридин, реагент Вільсмайєра-Хаака, перегрупування, рентгеноструктурне дослідження.

NOVEL EXAMPLES OF ELECTROPHILIC REARRANGEMENT OF SUBSTITUTED PYRIMIDIN-4-ONES UNDER VILSMEIER-HAACK REACTION CONDITION

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The critical influence of the size of aliphatic annulated cycles in 2,2-disubstituted pyrimidin-4-ones on the conditions of rearrangement under the action of Vilsmeier-Haack reagent was established. Compounds with a 5-membered ring cycle to pyrimidin-4-one require heating at 110^{0}C for 2 h due to the coplanar arrangement of dimethyliminium and chloriminium groups in intermediates, which leads to placement of a positive charge on the nitrogen atom of the dimethylamino group, which is unfavorable for the reaction. In the case of 6- and 7-membered annulated cycles, there is interatomic repulsion in the intermediates from the hydrogen atoms of methyl and methylene groups, as well as hydrogen atoms of CH and NH, which contributes to placement of a positive charge on the endocyclic atom of nitrogen and chloriminium salt and easier rearrangement. The size of aliphatic annealed and spirocycles to the pyrimidine framework affects not only the reaction conditions but also the formation of products.

Keywords: pyrimidin-4-one; substituted pyridine; Vilsmeier-Haack reagent; rearrangement; X-ray diffraction study.

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