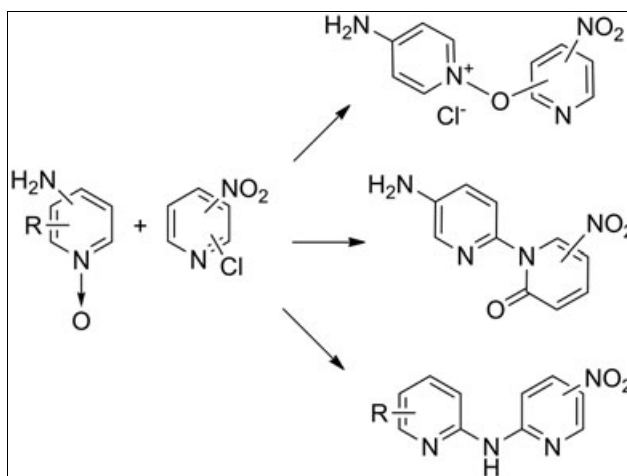Ewa Wolińska[a],* and Wiesław Pucko[b]

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Reaction of 2-aminopyridine *N*-oxides **1a–d** with chloronitropyridine **7a** gave 2-[(pyridin-2-yl)amino]pyridine *N*-oxides **8a–c** and **9** in good yield. The reactions of 4- and 3-aminopyridine *N*-oxides **12a,b** and **24** with **7a–c** proceed in the different manner involving initial formation of the intermediary 1-pyridyloxypyridinium salts **13a–d** and **26**, which rearrange to 4-[(5-nitropyridin-2-yl)amino]pyridine *N*-oxide **22** and 1-(3-aminopyridin-2-yl)pyrid-2-one derivatives **27a,b**, respectively. However, N-protected 2-aminopyridine *N*-oxides **17** gave quaternary 1-pyridyloxypyridinium salts **18a,b**, which upon treatment with aqueous ammonia afforded 2-[(pyridin-2-yl)amino]pyridine *N*-oxides **8a** and **20**. Quantum chemical calculations at the DFT/B3LYP/6-311++G(d,p) level were performed to explain the differences in properties of the frontal orbitals and atomic charge distribution in isomeric aminopyridine *N*-oxides.

INTRODUCTION

Some years ago, it was reported [2] that reaction of 2-aminopyridine *N*-oxide **1a** with unactivated 2-halogenopyridines **2a,b** under forcing conditions [3] provided 3-(2-pyridylamino)-2(1*H*)pyridone (**5**) as *cine* substitution product (Scheme 1). Compound **5** results from the nucleophilic attack by the *N*-oxide oxygen in **1a** on the carbon atom bearing halogen to form the cation **3**, which, in the presence of potassium carbonate, undergoes loss of proton and conversion to an anhydro base **4**, which by a [3,3′] sigmatropic shift and [1,5] H proton migration rearranges to **5**.

In contrast, activated 2-chloropyridines **2c,d**, containing the electron-withdrawing carboxy or cyano groups located at C-3 position, undergo substitution of halogen in the different manner leading to 2-[(pyridin-2-yl)amino]pyridine *N*-oxides **6c,d** exclusively (Scheme 1) [4,5]. The latter reaction has shown considerable synthetic utility and allows a highly efficient entry to functionalized 2,2′-dipyridylamine *N*-oxides, which may serve as intermediates to a variety of fused azaheteroaromatic systems possessing interesting pharmacological activity [6]. The formation of 2-[(pyridin-2-yl)amino]pyridine *N*-oxides **6** was supposed to proceed via direct nucleophilic substitution of halogen in compounds **2c,d** by amino group from 2-aminopyridine *N*-oxide **1a**, (S$_N$AE^{ipso} mechanism); although experimental data were not sufficient to make any generalization of this process. However, the recent work regarding a mild and high-yielding synthesis of *N*-(pyridin-2-yl)amides employing 2-aminopyridine *N*-oxide **1a** [7], as well as our theoretical calculations of electron densities at *N*-oxide and amino groups in isomeric aminopyridine *N*-oxides (see succeeding text), prompted us to reinvestigate more thoroughly the reactions of these systems with chloronitropyridines, to establish their relative reactivity toward electrophilic reagents.

RESULTS AND DISCUSSION

By analogy with previous studies [5], we have investigated the reaction of 2-aminopyridine *N*-oxides **1a–d** with

a commercially available 2-chloro-5-nitropyridine (**7a**). The reagents were kept in dry *N,N*-dimethylformamide (DMF) at 100–120°C in the presence of catalytic amount of potassium iodide (Scheme 2). The coupling reactions of **1a** and substituted 2-aminopyridine *N*-oxides **1b,c** proceeded smoothly, affording the corresponding nitro derivatives of 2,2′-dipyridylamine *N*-oxide **8a–c** in good yield. Interestingly, in the case of using 2-amino-6-methylpyridine *N*-oxide (**1d**), the major product was not expected to be a nitro derivative of 2,2′-dipyridylamine *N*-oxide **8d** but tripyridylamine *N*-oxide **9** formed with 75% yield. Its structure was clearly established by ¹H nmr and elemental analysis. Deoxygenation of **8a–c** and **9** by phosphorous trichloride in dry ethyl acetate afforded nitro derivatives of

dipyridylamines and tripyridylamines **10a–c** and **11** in moderate yield (Scheme 2). This reaction provides an easy access to functionalized 2,2′-dipyridylamines, which are available only by more sophisticated methods [8]. Encouraged by these promising results, we examined the preparation of various dipyridylamines by using 3-aminopyridine and 4-aminopyridine *N*-oxides.

The reactions of 3-aminopyridines and 4-aminopyridines without *N*-oxide functionality with chloronitropyridines were earlier investigated [9]; however, the yields of the desired nitro(pyridylamino)pyridines isolated from the reaction mixtures were very low. The reaction of 2-chloro-5-nitropyridine (**7a**) with an equivalent amount of 4-aminopyridine *N*-oxide (**12a**) either in DMF at 100°C or

Scheme 1. Reactions of 2-aminopyridine *N*-oxide **1a** with 2-halopyridines **2a–d**.

2a: R = H, X = Br
2b: R = H, X = Cl
2c: R = COOH, X = Cl
2d: R = CN, X = Cl

6c: R = COOH
6d: R = CN
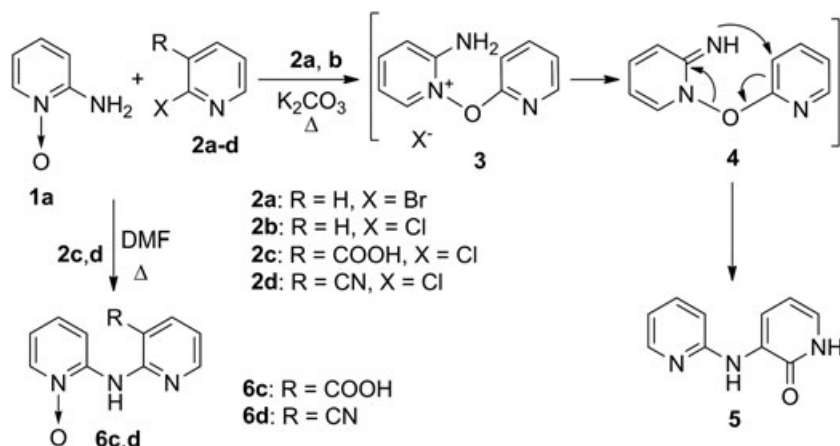
Scheme 2. Reactions of 2-aminopyridine *N*-oxides **1a–d** with 2-chloropyridine **7a**.

1a: R = H
1b: R = 4-CH₃
1c: R = 5-CH₃
1d: R = 6-CH₃

10a: R = H
10b: R = 4-CH₃
10c: R = 5-CH₃
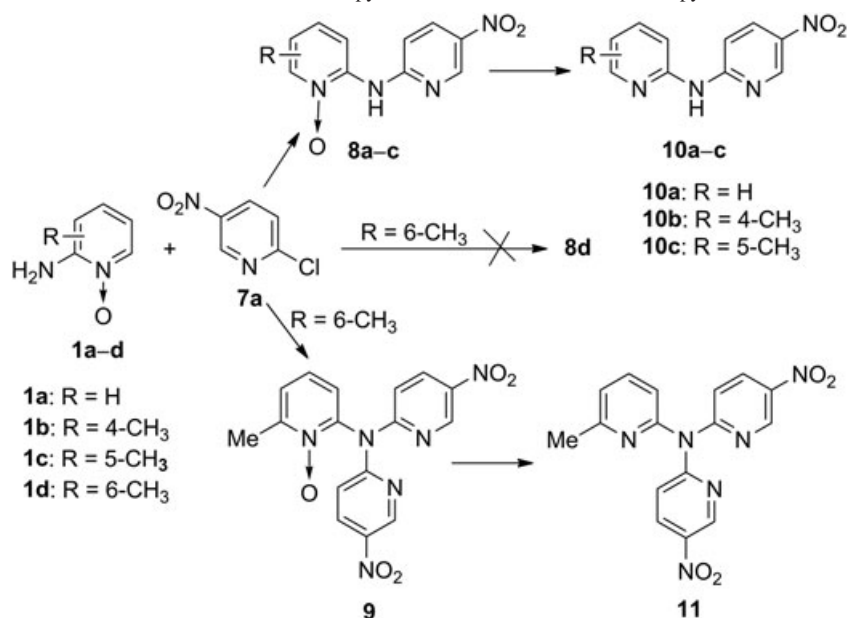
in boiling ethanol proceeded smoothly, affording the colorless precipitate in good yield. The product was easily purified by recrystallization from ethanol and identified by spectroscopic methods and microanalysis. The structure assignment of **13a** is based on its solubility in water, its ir spectrum featuring the presence of the amino group absorptions at 3350 and 1690 cm^{-1} and the ^{1}H nmr spectrum clearly showing the chemical shifts and multiplicity pattern of 4-amino-1-pyridyloxypyridinium chloride (Scheme 3). Formation of compound **14** in the reaction was not observed. To make sure that the amino group in **13a** does not play any role in the reaction with 2-chloropyridine, 4-(*N,N*-dimethylamino)pyridine *N*-oxide (**12b**) possessing a tertiary amino group was subjected to react with 2-chloro-5-nitropyridine (**7a**). The reaction gave 4-(*N,N*-dimethylamino)-1-[(5-nitropyridin-2-yl)oxy]pyridin-1-ium chloride (**13b**) in 51% yield. This result unequivocally proved that, under applied conditions, the amino group does not take part in the reaction. The nucleophilic attack by the *N*-oxide oxygen in **12a** and **12b** at activated pyridine ring, giving the corresponding 1-(pyridin-2-yl)oxy]pyridinium chlorides **13a** and **13b** was found as the only possible mechanism. Extending this study by using 2-chloro-3-nitropyridine (**7b**) and 4-chloro-3-nitropyridine (**7c**) showed the generality of this process, because the corresponding 4-amino-1-pyridinium chlorides **13c** and **13d** were obtained in 71–74% yield (Scheme 3). It is well known that reactions
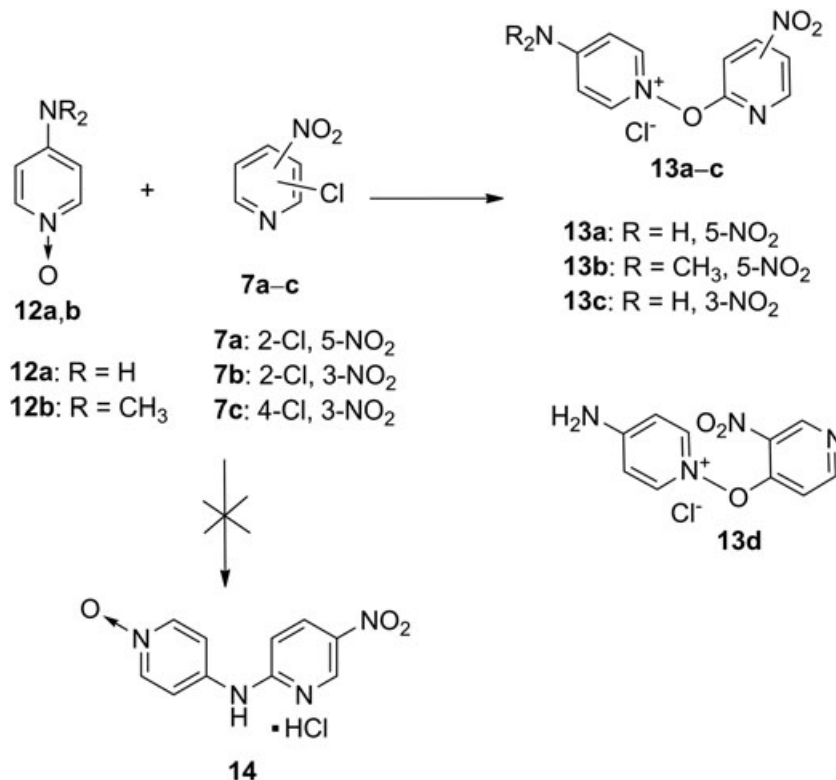
of pyridine *N*-oxides with alkylating agents afford the corresponding 1-alkoxypyridinium salts [10]. The results presented in this study clearly show that analogous quaternary salts may also be formed with some electrophilic heteroarenes.
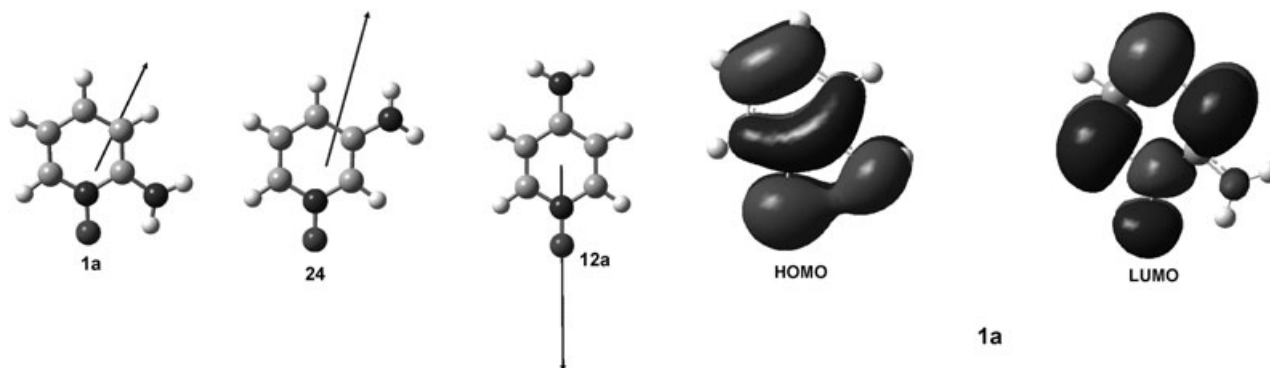
It is reasonable to assume that the formation of the 4-amino-1-pyridyloxypyridinium salts **13a–d** proceeds in preference to the expected 2-[(pyridin-4-yl)amino]pyridine *N*-oxide **14** as a consequence of the enhanced nucleophilicity of *N*-oxide oxygen atom in comparison with exocyclic amino nitrogen atom. To prove this, the structural and electronic characterizations of isomeric aminopyridine *N*-oxides **1a**, **12a**, and **24** were performed using theoretical calculation at the Density Functional Theory (DFT)/B3LYP/6-311++G(d,p) level. View of the molecules **1a**, **12a**, and **24** with the vectors of dipole moments obtained after energy minimization and geometrical parameters optimization is shown in Figure 1.

The theoretical calculation showed that, from among the analyzed isomers of aminopyridine *N*-oxide, isomer **1a** is the most energetically stable with relative energy of remaining isomers of about 6–7 kcal/mol with respect to isomer **1a** (Table 1).

To characterize the electronic structure of **1a**, **12a**, and **24**, the frontier orbitals, Natural Bond Orbitals (NBO), and Electrostatic Potential (ESP) atomic charges of the atoms, as the reactivity descriptors in the reaction of the nucleophilic substitution, were calculated at DFT/B3LYP/6-311++G(d,p) level. The distributions of the HOMO and

Scheme 3. Reactions of 4-aminopyridine *N*-oxides **12a,b** with chloropyridines **7a–c**.

13a: R = H, 5-NO$_2$
13b: R = CH$_3$, 5-NO$_2$
13c: R = H, 3-NO$_2$

12a: R = H
12b: R = CH$_3$

7a: 2-Cl, 5-NO$_2$
7b: 2-Cl, 3-NO$_2$
7c: 4-Cl, 3-NO$_2$

Figure 1. The molecular structures of **1a**, **24**, and **12a** with the vectors of dipole moments (origin in the center of mass) obtained from DFT/B3LYP/6-311++G(d,p) calculations.
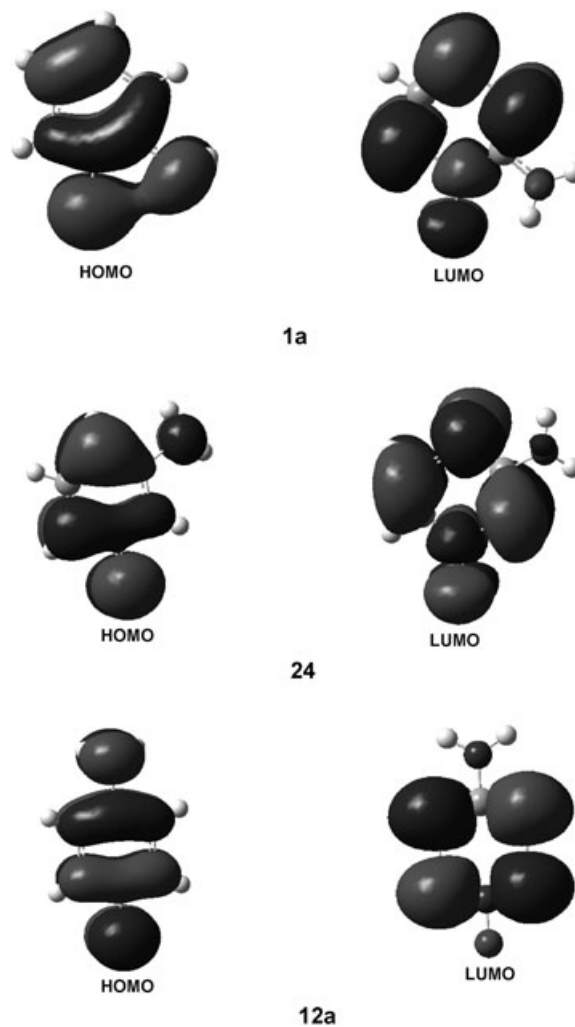
Table 1

Total Density Functional Theory (DFT) molecular energies E (au), relative energies ΔE (kcal/mol), and dipole moments D_m (D) calculated at DFT/B3LYP/6-311++G(d,p) level.

Compound	E	ΔE	D_m
1a	−378.92709985	0	3.974
24	−378.91706834	6.295	5.388
12a	−378.91545503	7.307	6.976

LUMO orbitals for the investigated compound are presented on Figure 2. The highest occupied molecular orbitals (HOMOs) for **1a**, **12a**, and **24** and the lowest unoccupied molecular orbitals for **1a** and **24** are localized practically on the all non-H atoms of the molecules, whereas the LUMO orbital in **12a** is formed without the contribution of the atomic orbitals of heteroatoms. The energies of HOMO and LUMO orbitals are given in Table 2. The values of the energy separation between the HOMO and LUMO indicate that the structures of **1a**, **12a**, and **24** are very stable. However, the HOMO–LUMO energy gap for **12a** (98.068 kcal/mol) is somewhat lower than the energy gaps for **1a** (102.341 kcal/mol) and **24** (102.341 kcal/mol). Similarly, the first ionization potential for **12a** of 122.622 kcal/mol is distinctly lower than those calculated for **1a** and **24** of 131.909 and 138.366 kcal/mol, respectively. The indicated differences in properties of the frontal orbitals for molecules **1a** and **24** comparing with the properties observed in the molecule **12a** can be a reason of differences in their reactivity.

The selected values of the atomic charges for heteroatoms are shown in Table 3. One can see that the NBO charge distribution on atoms is very similar in all analyzed molecules giving, independently from the amino group position, somewhat larger (in absolute value) negative charge at *N*-amino atom in comparison with the charge at *N*-oxide O atom. The atomic charge calculated using ESP method shows one important difference in its distribution

Figure 2. Schematic drawings of the HOMO and LUMO orbitals of **1a**, **24**, and **12a** as calculated using DFT/B3LYP/6-311++G(d,p) method.

Table 2

The energies of the frontal orbitals HOMO, E_{HOMO} (kcal/mol), LUMO, E_{LUMO} (kcal/mol), and HOMO–LUMO energy gap, $\Delta E_{HOMO-LUMO}$ (kcal/mol), calculated at DFT/B3LYP/6-311++G(d,p) level.

Compound	E_{HOMO}	E_{LUMO}	$\Delta E_{HOMO-LUMO}$
1a	−131.909	−29.568	102.341
24	−138.366	−32.907	102.341
12a	−122.622	−24.554	98.068

in **1a** and **24** versus **12a**: the negative charge at O atom in **12a** is larger (in absolute value) than that at *N*-amino atom, whereas in **1a** and **24**, the opposite relation is observed.

In the light of the results presented in Table 3, the total electron charge that is accepted by the *N*-oxide oxygen atom in 2-aminopyridine *N*-oxide (**1a**) is only somewhat smaller than the electron charge located at the amino group. Taking this into consideration, it is not astonishing

Table 3

Natural Bond Orbitals (NBO) and Electrostatic Potential (ESP) atomic charges calculated at DFT/B3LYP/6 311++G(d,p) level.

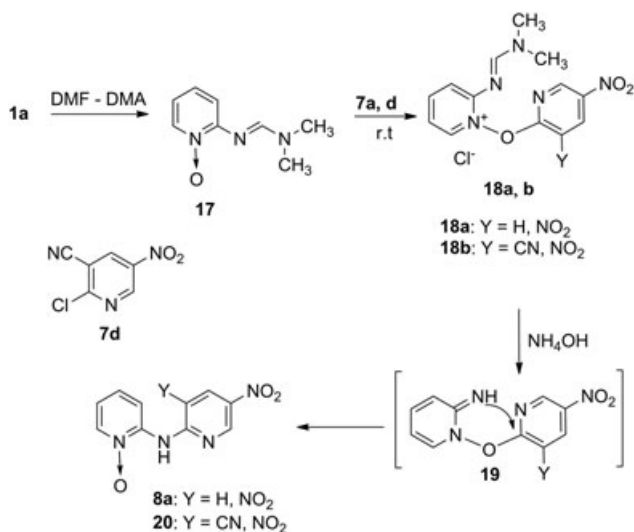| Compound	NBO			ESP		
	NH$_2$	N-pyridine	O	NH$_2$	N-pyridine	O
1a	−787	+12	−603	−974	+287	−595
24	−780	+80	−538	−787	+508	−584
12a	−787	+29	−583	−1698	+3849	−1781

to assume that reaction between **1a** and 2-chloro-5-nitropyridine (**7a**) may occur via two alternative pathways, one involving a primary nucleophilic attack by the N-oxide oxygen and the other one by amine nitrogen (Scheme 4, routes *a* and *b*). Although the first of these mechanistic considerations did not seem to be in accordance with experimental finding, its contribution to the amination reaction should also be considered. If route *a* is operative, it will involve an initial formation of 2-amino-1-pyridyloxypyridinium chloride **15**, which will react further into **8a** by intramolecular nucleophilic attack of the amino group on C-2 carbon atom. In case of route *b*, compound **8a** will be formed via a direct nucleophilic attack by amino group involving intermediary σ-adduct **16** (Scheme 4).

To find an experimental support for this first supposition, compound **17** with protected amino group was prepared from 2-aminopyridine N-oxide (**1a**) and DMF/DMA and reacted with 2-chloro-5-nitropyridine (**7a**) in DMF at room temperature. The protection of amino group in **17** excludes the possibility of direct nucleophilic attack

of amine according to mechanism *b* presented on Scheme 4. Under these reaction conditions, compound **17** undergoes coupling with **7a** to give the corresponding quaternary pyridinium salt **18a** in 71% yield (Scheme 5). The compound **18a** was sufficiently stable to be isolated in pure state and could be characterized by ir, ^{1}H nmr, ms, and hrms spectra. Similarly, the reaction of **17** with 2-chloro-3-cyano-5-nitropyridine (**7d**) under the same reaction conditions afforded the expected pyridyloxypirydinium salt **18b** in good yield.
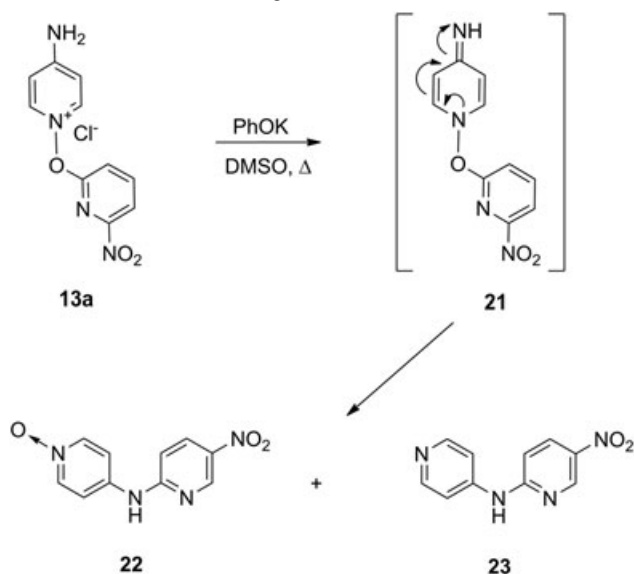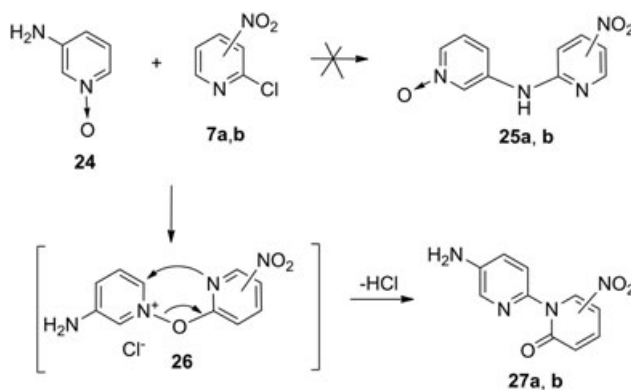
When we allowed compound **18a** to react with aqueous ammonia at room temperature, we found that 2-(5-nitro-2-pyridylamino)pyridine N-oxide (**8a**) was immediately formed in 80% yield. A similar process also occurs in the reaction of **18b** with aqueous ammonia to give 2-(3-cyano-5-nitro-2-pirydylamino)pyridine N-oxide (**20**). These results prove that base-induced hydrolysis of carbon–nitrogen double bonds in quaternary pyridinium salts **18a,b** leads to the formation of the corresponding unprotected intermediates **19**, which by intramolecular nucleophilic attack of the free imino group on C-2 carbon

Scheme 4. Two possible mechanistic pathways of the formation of **8a**.
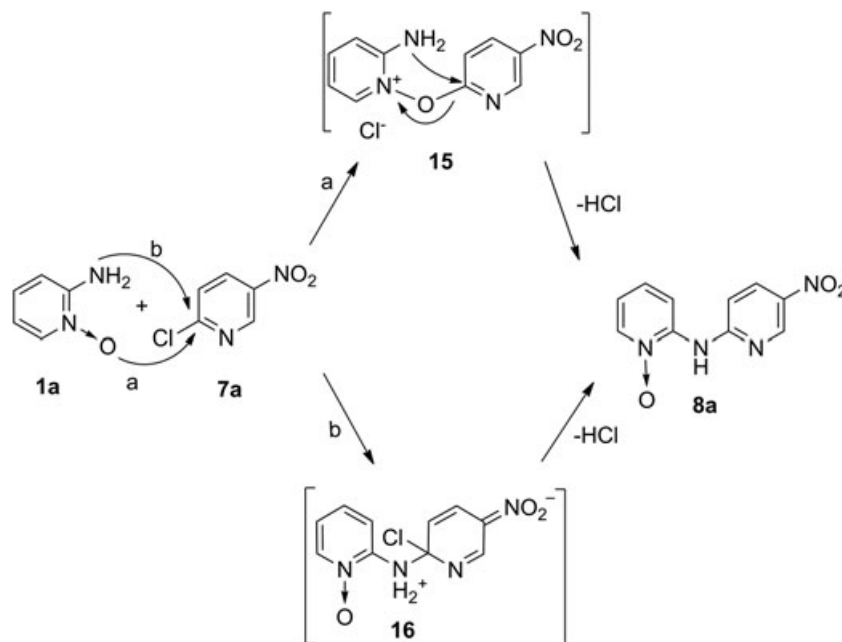
Scheme 5. Reactions of N-protected 2-amino *N*-oxide **17** with **7a**,**d**.

18a: Y = H, NO₂
18b: Y = CN, NO₂

8a: Y = H, NO₂
20: Y = CN, NO₂

Scheme 7. Reactions of 3-aminopyridine *N*-oxide **24** with 2-chloropyridines **7a**,**b**.

27a, b

yields 2,2′-dipyridylamine *N*-oxides **8a** and **20**. This result may also suggest that amination reactions of activated chloronitropyridines by 2-aminopyridine *N*-oxides also proceeds via intermediary quaternary pyridinium salts (route *a*) as indicated in Scheme 4.

The reaction of 4-aminopyridyloxypyridinium chloride **13a** with ammonium hydroxide was unsuccessful. However, treatment of **13a** with potassium fenolate in dimethyl sulfoxide in high temperature gave **22** and **23** in 28 and 10% yields (Scheme 6). The formation of **22** might be rationalized by initial base-catalyzed proton abstraction

from the amino group in **13a** to give an anhydro base **21**, which by sigmatropic shifts could rearrange to the compound **22**. The thermal deoxygenation of **22** into **23** is in line with known pyridine *N*-oxide chemistry [11].

To complete our study on amination of chloronitropyridines, we tried to use 3-aminopyridine *N*-oxide (**24**) as a starting material. The reaction of 2-chloro-5-nitropyridine (**7a**) and 2-chloro-3-nitropyridine (**7b**) with **24** in DMF at 100°C did not give amination products **25a**,**b**. Only corresponding 1-(2-pyridyl)-2-pyridone derivatives **27a**,**b** were obtained in low yields via intermediary 3-amino-1-pyridyloxypyridinium salt **26** (Scheme 7) [12]. The exclusive formation of **27a**,**b** instead of **25a**,**b** lends further support to a suggestion that reactions of isomeric aminopyridine *N*-oxides with electrophilic chloro(nitro)pyridines proceed via a primary nucleophilic attack of *N*-oxide oxygen atom on carbon atom bearing halogen.

Scheme 6. Rearrangement of **13a** into **22** and **23**.

13a   **21**

22   +   **23**

CONCLUSIONS

Our findings reveal that isomeric 2-aminopyridine, 3-aminopyridine and 4-aminopyridine *N*-oxides may react with electrophilic chloronitropyridines at either oxygen or amino nitrogen atoms. The different reaction courses specifically depend on the position of an amino substituent in the pyridine *N*-oxide ring. The reactions of 3- and 4-aminopyridine *N*-oxides with these electrophiles proceed via initial formation of the intermediary 1-pyridyloxypyridinium salts. On the other hand, the reaction of 2-aminopyridine *N*-oxide gives 2,2′-dipyridylamine *N*-oxides exclusively. However, *N*-protected 2-aminopyridine *N*-oxides are reacted with chloronitropyridines in the different manner giving quaternary 1-pyridyloxypyridinium salts, which easily undergo base-catalyzed rearrangement upon treatment with aqueous ammonia. This novel route to 2,2′-dipyridylamine *N*-oxides and other biheterocyclic amines is currently under investigation, and the results will be reported in due course.

EXPERIMENTAL

General. Nmr spectra were recorded on Varian Gemini (Palo Alto, CA) and Jeol JNM-4H-100 (Jeol,Tokyo, Japan) spectrometers, at 200 and 400 MHz for ^{1}H nmr and 50 and 100 MHz for ^{13}C nmr. Chemical shifts (δ) are given in parts per million, and coupling constants are given as absolute values expressed in Hertz. Ir spectra were determined in KBr with a Unicam SP-200 (Unicam, Cambridge, UK) apparatus. Mass spectra were obtained using AMD 604 (AMD Intectra GmbH, Germany) spectrometer. Elemental analyses were recorded with a PerkinElmer 2400-CHN (PerkinElmer, Waltham, MA) analyzer, and the results for indicated elements were within 0.3% of the calculated values. Thin-layer chromatography was carried out on aluminum sheets precoated with silica gel 60 F_{254} (Merck Warsaw, Poland). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.060 mm). The solvents were dried and distilled according to standard procedures. All reagents were purchased from Aldrich (Sigma--Aldrich, Poznan, Poland).

General procedure for the preparation of compounds 8a–c and 9. A mixture of 2-aminopyridine *N*-oxide **1a–d** (11 mmol), 2-chloro-5-nitropyridine **7a** (10 mmol), and catalytic amount of potassium iodide in dry DMF (20 mL) was heated at 100–120°C for 2 h. After cooling, the precipitate was filtered and recrystalized from ethanol/water mixture.

2-[(5-Nitropyridin-2-yl)amino]pyridine *N*-oxide (8a). Yield: 1.73 g, 58%, mp 285–286°C; ir (KBr): 3220 (NH), 1530, 1330 (NO$_2$), 1200 (N$^+$–O$^-$) cm^{-1}; ^{1}H nmr (100 MHz, CDCl$_3$): δ 6.93–7.03 (m, 2H), 7.36–7.45 (m, 1H), 8.28–8.32 (m, 1H), 8.42 (dd, *J* = 9.1, 2.7 Hz, 1H), 8.86 (dd, *J* = 8.7, 1.9 Hz, 1H), 9.24 (d, *J* = 2.7 Hz, 1H), 10.28 (s, 1H);. [13]C nmr (100 MHz, CF$_3$COOH–C$_6$D$_6$): δ 114.9, 118.4, 120.6, 136.6, 139.6, 140.8, 141.7, 142.8, 145.6, 154.4. *Anal.* Calcd for C$_{10}$H$_8$N$_4$O$_3$: C, 51.73; H, 3.47; N, 24.13. Found: C, 51.68; H, 3.36; N 24.28.

2-[(5-Nitropyridin-2-yl)amino]-4-methylpyridine *N*-oxide (8b). Yield: 1.82 g, 74%, mp 272–275°C; ir (KBr): 3150 (NH), 1500, 1330 (NO$_2$), 1200 (N$^+$–O$^-$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.6 (s, 3H), 7.2 (dd, *J* = 6.25, 2.0 Hz, 1H), 7.45 (d, *J* = 8.75 Hz, 1H), 8.05–8.35 (m, 2H), 8.55 (dd, *J* = 8.75, 2.0 Hz, 1H), 9.05 (d, *J* = 2.5 Hz, 1H). *Anal.* Calcd for C$_{11}$H$_{10}$N$_4$O$_3$: C, 53.66; H, 4.09; N 22.75. Found: C, 53.55; H, 3.96; N 22.56.

2-[(5-Nitropyridin-2-yl)amino]-5-methylpyridine *N*-oxide (8c). Yield: 2.31 g, 94%, mp 278–279°C; ir (KBr): 3200 (NH), 1500, 1340 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.5 (s, 3H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.85 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.15–8.35 (m, 2H), 8.55 (dd, *J* = 8.7, 2.0 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H). *Anal.* Calcd for C$_{11}$H$_{10}$N$_4$O$_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.67; H, 3.97; N, 22. 62.

2-[Bis(5-nitropyridin-2-yl)amino]-6-methylpyridine *N*-oxide (9). Yield: 1.38 g, 75%, mp 218–220°C; ir (KBr): 1520, 1510, 1345, 1340 (NO$_2$), 1270 (N$^+$–O$^-$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.7 (s, 3H), 7.15–8.30 (m, 5H), 8.55 (dd, *J* = 7.5, 2.0 Hz, 2H), 9.16 (d, *J* = 2.0 Hz, 2H). *Anal.* Calcd for C$_{16}$H$_{12}$N$_6$O$_5$: C, 52.18; H, 3.28; N, 22.82. Found: C, 52.28; H, 3.08; N, 22.72.

General procedure for the preparation of compounds 10a–c and 11. A mixture of **8a–c**, **9** (5 mmol) and PCl$_3$ (10 mmol) in dry ethyl acetate (50 mL) was refluxed for 1 h. The mixture was cooled, and the precipitate was filtered off and washed with 10% K$_2$CO$_3$ and water. The product was recrystallized from ethanol.

2-[(5-Nitropyridin-2-yl)amino]pyridine (10a). Yield: 0.35 g, 34%, mp 187–188°C; Lit. [13]. mp 188–189°C.

2-[(5-Nitropyridin-2-yl)amino]-4-methylpyridine (10b). Yield: 0.39 g, 34%, mp 185–187°C; ir (KBr): 3100 (NH), 1510, 1340 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.45 (s, 3H), 7.17 (d, *J* = 8.75 Hz, 1H), 7.32 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40–8.10 (m, 2H), 8.45 (dd, *J* = 8.75, 2.5 Hz, 1H), 9.05 (d, *J* = 2.5 Hz, 1H); ^{13}C nmr (100 Hz, CDCl$_3$): δ 21.3, 110.3, 113.3, 119.8, 133.3, 138.1, 145.6, 147.6, 149.7, 152.4, 157.4. *Anal.* Calcd for C$_{11}$H$_{10}$N$_4$O$_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.14; H, 4.33; N, 24.78.

2-[(5-Nitropyridin-2-yl)amino]-5-methylpyridine (10c). Yield: 0.32 g, 28%, mp 195–196°C; ir (KBr): 3100 (NH), 1500, 1330 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.70 (s, 3H), 7.30–7.60 (m, 3H), 8.22 (d, *J* = 7.5 Hz, 1H), 8.75 (dd, *J* = 7.50, 2.50 Hz, 1H), 9.35 (d, *J* = 2.5 Hz, 1H). [13]C nmr (100 MHz, DMSO-*d*$_6$): δ 17.1, 113.1, 114.1, 127.8, 128.0, 132.9, 136.9, 138.1, 141.9, 144.8, 157.1. *Anal.* Calcd for C$_{11}$H$_{10}$N$_4$O$_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.36; H, 4.32; N, 24.30.

2-[Bis(5-nitropyridin-2-yl)amino]-6-methylpyridine (11). Yield: 0.34 g, 19%, mp 185–186°C; ir (KBr): 1525, 1510, 1350, 1310 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 2.85 (s, 3H), 7.0 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.10–7.30 (m, 4H), 7.52 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.17 (t, *J* = 8.5 Hz, 1H), 8.65 (dd, *J* = 8.5, 2.0 Hz, 2H). [13]C nmr (100 MHz, CDCl$_3$): δ 24.2, 116.5, 119.2, 122.8, 132.9, 139.3, 140.2, 144.9, 154.4, 159.5, 159.9. *Anal.* Calcd for C$_{16}$H$_{12}$N$_6$O$_4$: C, 54.55; H, 3.43; N, 23.85. Found: C, 54.81; H, 3.35; N, 23.69.

General procedure for the preparation of compounds 13a–d. A mixture of chloronitropyridines **7a–c** (10 mmol) and 4-aminopyridine *N*-oxides **12a,b** (10 mmol) in ethanol or DMF (20 mL) was heated for 3 h. The crude products **13a–d** were isolated and purified as described in the following text.

4-Amino-1-[(5-nitropyridin-2-yl)oxy]pyridin-1-ium chloride (13a). The product was obtained in ethanol. After cooling, the precipitate was filtered, and the crude product was recrystallized from ethanol. Yield: 2.2 g, 82%, mp 221–222°C; ir (KBr): 3350, 3150, 1650 (NH$_2$), 1540, 1350 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 7.17 (d, *J* = 6.25 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 6.25 Hz, 2H), 8.81 (dd, *J* = 8.0, 2.5 Hz, 1H), 9.07 (d, *J* = 2.50 Hz, 1H). *Anal.* Calcd for C$_{10}$H$_9$N$_4$O$_3$Cl: C, 44.71; H, 3.38; N, 20.85. Found: C, 44.87; H, 3.34; N, 21.18.

4-(*N*,*N*-Dimethylamino)-1-[(5-nitropyridin-2-yl)oxy]pyridin-1-ium chloride (13b). The product was obtained in boiling ethanol. After cooling, the solvent was evaporated *in vacuo*, and acetone was added to the residue. The precipitate was filtered and recrystallized from methanol/acetone mixture. Yield: 1.5 g, 50.5%, mp 157–158°C; ir (KBr): 1535, 1350 (NO$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 3.1 (s, 6H), 6.9 (d, *J* = 8.7 Hz, 2H), 7.3 (d, *J* = 10 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 8.75 (dd, *J* = 10.0, 3.0 Hz, 1H), 8.9 (d, *J* = 3.0 Hz, 1H). *Anal.* Calcd for C$_{12}$H$_{13}$N$_4$O$_3$Cl × H$_2$O: C, 45.80; H, 4.80; N, 17.80. Found: C, 46.06; H, 4.64; N, 17.84.

4-Amino-1-[(3-nitropyridin-2-yl)oxy]pyridin-1-ium chloride (13c). The product was obtained in boiling ethanol. After cooling, the precipitate was filtered, and the crude product was recrystallized from ethanol/water mixture. Yield: 2.0 g, 74%; mp 208–210°C; ir (KBr): 3300, 3150, 1640 (NH$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ 7.05 (d, *J* = 7.5 Hz, 2H), 7.45 (dd, *J* = 5.0, 7.5 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 8.35 (d, *J* = 5.0 Hz, 1H), 8.53 (d, *J* = 7.5 Hz, 1H). *Anal.* Calcd for C$_{10}$H$_9$N$_4$O$_3$Cl: C, 44.71; H, 3.38; N, 20.85. Found: C, 44.71; H, 3.30; N, 20.64.

4-Amino-1-[(3-nitropyridin-4-yl)oxy]pyridin-1-ium chloride (13d). The product was obtained by heating DMF at 100°C. After cooling, the precipitate was filtered, and the crude product was recrystallized from ethanol/water mixture. Yield: 1.9 g, 71%, mp 190–191°C; ir (KBr) 3350, 3150, 1640 (NH$_2$), 1530, 1340

(NO_2) cm^{-1}; ^{1}H nmr (200 MHz, CF$_3$COOD): δ 6.77 (d, $J = 7.5$ Hz, 2H), 7.92 (d, $J = 7.5$ Hz, 2H), 8.27 (d, $J = 6.25$ Hz, 1H), 8.95 (d, $J = 6.25$ Hz, 1H), 9.42 (s, 1H). *Anal.* Calcd for C$_{10}$H$_9$N$_4$O$_3$Cl: C, 44.71; H, 3.38; N, 20.85. Found: C, 44.64; H, 3.45; N, 20.81.

General procedure for the preparation of 2-{[(*N,N*-dimethylamino)methylene]amino}pyridine *N*-oxide (17). A mixture of 2-aminopyridine *N*-oxide **1a** (10 mmol) and DMF–DMA (2 mL, 15 mmol) was stirred at room temperature for 12 h. The precipitate was filtered off, washed with ethyl ether, and dried in a dessicator over P$_2$O$_5$. Analytical sample of the product was recrystallized from chloroform/hexane mixture.

*2-{[(*N,N*-Dimethylamino)methylene]amino}pyridine *N*-oxide (17).* Yield 1.48 g, 90%, mp 132–133°C; ^{1}H nmr (400 MHz, CDCl$_3$): δ 3.08 (s, 3H), 3.09 (s, 3H), 6.72-6.76 (m, 1H), 6.93 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.94–7.15 (m, 1H), 8.09 (dd, $J = 6.8$, 1.2 Hz, 1H), 9.07 (s, 1H). ^{13}C nmr (100 MHz, CDCl$_3$): δ 34.1, 40.8, 117.2, 120.3, 127.7, 139.8, 152.9, 156.8. hrms (EI). Calcd for C$_8$H$_{11}$N$_3$O: $m/z = 165.09021$. Found: $m/z = 165.09021$.

General procedure for the preparation of quaternary pyridinium salts 18a,b. 2-Chloropyridines **7a,d** (1 mmol) were added to the solution of 2-{[[(*N,N*-dimethylamino) methylene]amino}pyridine 1-oxide (**17**) (0.165 g,1 mmol) in DMF or acetonitrile (2 mL). The mixture was stirred at room temperature for 12 h. The hydroscopic products was filtered off, washed with anhydrous ethyl ether, and dried in a dessicator over P$_2$O$_5$.

*2-{[(*N,N*-Dimethylamino)methylene]amino}-1-[(5-nitropyridin-2-yl)oxy]pyridin-1-ium chloride (18a).* Yield 0.23 g, 71%, mp 161–162°C; ^{1}H nmr (200 MHz, DMSO-d_6): δ 2.76 (s, 3H), 3.19 (s, 3H), 7.35–7.40 (m, 1H), 7.70 (dd, $J = 9.0$, 0.5 Hz, 1H), 7.99 (dd, $J = 9.0$, 1.5 Hz, 1H), 8.25–8.29 (m, 1H), 8.82 (s, 1H), 8.83 (dd, $J = 9.0$, 2.7 Hz, 1H), 8.93 (dd, $J = 7.0$, 1.5 Hz, 1H), 9.04 (dd, $J = 2.7$, 0.5 Hz, 1H). hrms (EI). Calcd for (C$_{13}$H$_{13}$N$_5$O$_3$)$^+$: $m/z = 287.1018$. Found: $m/z = 287.1019$. *Anal.* Calcd for C$_{13}$H$_{14}$N$_5$O$_3$Cl × 0.5H$_2$O: C, 46.92; H, 4.54; N, 21.04. Found: C, 47.05; H, 4.40; N, 20.97.

*1-[(3-Cyano-5-nitropyridin-2-yl)oxy]-2-{[(*N,N*-dimethylamino) methylene]amino}pyridin-1-ium chloride (18b).* Yield: 0.29 g, 85%, mp 150–151°C; ^{1}H nmr (200 MHz, DMSO-d_6): δ 2.82 (s, 3H), 3.24 (s, 3H), 7.36–7.44 (m, 1H), 8.04 (dd, $J = 8.97$, 1.5 Hz, 1H), 8.25–8.33 (m, 1H), 8.89 (s, 1H), 9.95 (dd, $J = 6.93$, 1.5 Hz, 1H), 9.29 (d, $J = 2.60$ Hz, 1H), 9.58 (d, $J = 2.60$ Hz, 1H). ^{13}C nmr (100 MHz, DMSO-d_6): δ 35.1, 41.5, 95.1, 111.7, 116.2, 117.9, 138.9, 141.7, 142.2, 144.2, 148.0, 154.9, 159.6, 163.3. hrms (EI). Calcd for (C$_{14}$H$_{13}$N$_6$O$_3$)$^+$: $m/z = 313.10491$. Found: $m/z = 313.10497$.

General procedure for the rearrangement of chlorides 18a, b into 8a and 20. To the solution of appropriate chloride **18a,b** (1 mmol) in anhydrous ethanol (6 mL), 25% ammonia (0.3 mL) was added. The mixture was stirred at room temperature for 5 min. The obtained solid was filtered off. The product was recrystallized from ethanol.

*2-[(5-Nitropyridyn-2-yl)amino]pyridine *N*-oxide (8a).* Yield: 0.186 g, 80%.

*2-[(3-Cyano-5-nitropyridyn-2-yl)amino]pyridine *N*-oxide (20).* Yield: 0.031 g, 12%, mp 257–258°C. ir (KBr): 3110 (NH), 2220 (CN); ^{1}H nmr (400 MHz, DMSO-d_6): δ 7.20–7.28 (m, 1H), 7.53–7.62 (m, 1H), 8.50–8.54 (m, 1H), 8.64–8.67 (m, 1H), 9.21 (d, $J = 2.8$ Hz, 1H), 9.38 (d, $J = 2.8$ Hz, 1H), 11.01 (s, 1H). ^{13}C nmr (100 MHz, DMSO-d_6): δ 96.1, 114.0, 114.3, 119.4, 127.9, 137.0, 137.5, 138.5, 143.1, 148.6, 155.7. *Anal.* Calcd for C$_{11}$H$_7$N$_5$O$_3$: C, 51.37; H, 2.74; N, 27.23. Found: C, 51.32; H, 2.77; N, 27.09.

Rearrangement of chloride 13a into 22 and 23. A mixture of **13a** (1 g, 3.7 mmol) and potassium phenoxide (0.49 g, 3.7 mmol) in DMSO (10 mL) was heated at 150°C for 30 min. After cooling, ice water was added, and the precipitate was filtered off. The products were separated by column chromatography with the use of benzene/acetone/methanol mixture (8:1:1).

*4-[(5-Nitropyridin-2-yl)amino]pyridine *N*-oxide (22).* Yield 0.25 g, 28%, mp over 315°C (dec); ir (KBr): 3200, 2800 (NH), 1500, 1340 (NO$_2$), 1200 (N$^+$–O$^-$); ^{1}H nmr (100 MHz, CF$_3$COOD): δ 7.17 (d, $J = 8.75$ Hz, 1H), 8.11 (d, $J = 7.5$ Hz, 2H), 8.47 (dd, $J = 8.75$, 2.5 Hz, 1H), 8.65 (d, $J = 7.5$ Hz, 2H), 9.02 (d, $J = 2.5$ Hz, 1H); ^{13}C nmr (100 MHz, CF$_3$COOD) δ 114.2, 116.0, 136.7, 140.9, 141.2, 143.6, 151.6, 155.6. *Anal.* Calcd for C$_{10}$H$_8$N$_4$O$_3$ × H$_2$O: C, 48.00; H, 4.02; N, 22.39. Found: C, 47.85; H, 3.95; N, 22.34.

4-[(5-Nitropyridin-2-yl)amino]pyridine (23). Yield 0.08 g, 10 %, mp over 305°C (dec); ir (KBr): 3100, 2800 (NH), 1500, 1330 (NO$_2$). ^{1}H nmr (100 MHz, CF$_3$COOD): δ = 7.07 (d, $J = 10$ Hz, 1H), 8.07 (d, $J = 7.5$ Hz, 2H), 8.45 (d, $J = 7.5$ Hz, 2H), 8.72 (dd, $J = 10.0$, 2.5 Hz, 1H), 9.30 (d, $J = 2.5$ Hz, 1H). ^{13}C nmr (100 MHz, CF$_3$COOD) δ = 114.5, 114.9, 137.4, 140.9, 141.9, 142.9, 154.4, 154.5 ppm. *Anal.* Calcd for C$_{10}$H$_8$N$_4$O$_2$: C, 55.55; H, 3.73. Found: C, 55.45; H, 3.76.

General Procedure for the preparation of pyridinones 27a,b. A mixture of 3-aminopyridine *N*-oxide (**24**) (1.1 g, 10 mmol) and appropriate 2-chloro-5/3-nitropyridine **7a,b** (1.6 g, 10 mmol) in DMF (20 mL) was heated at 100°C for 5 h. The solvent was evaporated under *vacuo*. The product was purified by column chromatography with the use of CHCl$_3$/acetone (8:1 and 1:1) and recrystallized from ethanol.

5-Nitro-1-(5-aminopyridin-2-yl)pyrid-2-one (27a). Yield: 0.20 g, 8.6%, mp 249–250°C; ir (KBr): 3450, 3350 (NH$_2$), 1680 (C=O), 1630 (NH$_2$) cm^{-1}; ^{1}H nmr (100 MHz, CF$_3$COOD): δ = 7.07 (d, $J = 9.5$ Hz, 1H), 7.95 (dd, $J = 8.75$, 5.0 Hz, 1H), 8.12 (d, $J = 8.75$ Hz, 1H), 8.35 (d, $J = 5.0$ Hz, 1H), 8.55 (m, 1H), 8.98 (d, $J = 2.5$ Hz, 1H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 120.0, 123.9, 125.9, 130.8, 133.7, 135.7, 136.9, 140.4, 141.5, 160.1. *Anal.* Calcd for C$_{10}$H$_8$N$_4$O$_3$: C, 51.73; H, 3.47; N, 24.13. Found: C, 51.73; H, 3.38; N, 23.91.

3-Nitro-1-(5-aminopyridin-2-yl)pyrid-2-one (27b). Yield: 0.15 g, 6.5%, mp 234–235°C; ^{1}H nmr (200 MHz, CF$_3$COOD): δ 6.87 (dd, $J = 8.7$, 6.2 Hz, 1H), 7.70–8.10 (m, 3H), 7.92 (dd $J = 6.2$, 1.3 Hz, 1H), 8.17 (dd, $J = 8.7$, 2.0 Hz, 1H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 104.1, 123.6, 125.8, 135.6, 137.2, 139.0, 139.8, 140.4, 146.2, 153.2. *Anal.* Calcd for C$_{10}$H$_8$N$_4$O$_3$: C, 51.73; H, 3.47; N, 24.13. Found: C, 51.78; H, 3.55; N, 24.00.

Theoretical calculation. The theoretical calculations at the DFT/B3LYP level with 6-311++G(d,p) basis set implemented in Gaussian 03 [14] were carried out to investigate the energetic, structural, and electronic parameters of **1a**, **12a**, and **24**. The structures were fully optimized without any symmetry constraint. The initial geometries were built *de novo* using the AM1 semi-empirical SCF-MO method implemented in the program package HyperChem version 4.5 [15].

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