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Mild and efficient addition of carbon nucleophiles to condensed pyridines: influence of structure and limits of applicability

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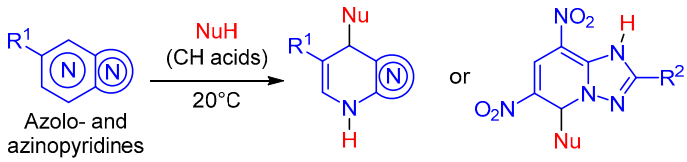


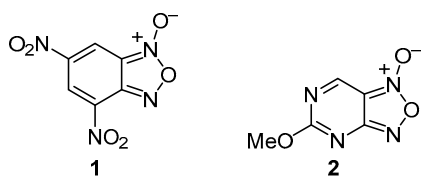
R^1 = NO_2, CO_2Me, Cl, Br, CF_3; R^2 = H, 4-$MeOC_6H_4$

A number of azolo- and azinopyridines with varying substituents and annulated heterocycles were synthesized and examined in dearomatization reactions with carbon nucleophiles. Depending on the structure, the resulting covalent σ-adducts were formed either under base-free conditions or in Et_3N-promoted process to give functionalized condensed dihydropyridines. Quantum-chemical calculations of the global electrophilicity index derived from FMO energies of azolopyridine series were performed to explain reactivity toward neutral and anionic C-nucleophiles. These values may be useful for qualitative prediction of particular reactivity pattern.

Keywords: carbon nucleophiles, condensed pyridines, nitrogen heterocycles, dearomatization, nucleophilic addition.

Electron-deficient aromatic and heteroaromatic compounds have been extensively studied during past few decades due to their interesting, sometimes exceptional properties. Many monographs and reviews were dedicated to the formation and reactivity of stable anionic σ-complexes and covalent σ-adducts of electrophilic aromatics and nucleophiles.[1] It is well known that annulation of a strong π-deficient heterocycle (furoxan, furazan, selenadiazole, etc.) significantly increases π-deficiency of the aromatics. Such compounds possess extremely high reactivity toward nucleophiles, therefore, a special term "superelectrophile" was coined in order to distinguish them from other electrophilic aromatics.[2] For example, 4,6-dinitrobenzofuroxan (**1**) (Fig. 1) was found to be more electrophilic than 4-nitrobenzenediazonium cation in reactions with nucleophilic indoles and pyrroles.[3] It also reacts with various types of neutral O-, S- and C-nucleophiles.[4] Recently Remennikov et al. reported another highly reactive neutral electrophile, namely, 5-methoxyfuroxano[3,4-*d*]pyrimidine (**2**) which formed stable adducts with enamines, silyl ethers, and other related compounds.[5]

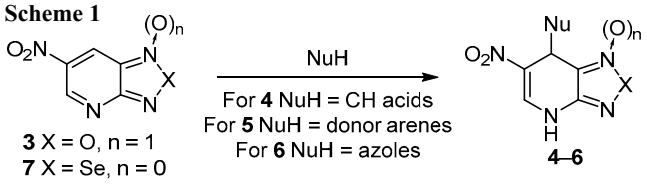
Previously, we have found that some aza analogs of furoxan **1** possess similar reactivity and the covalent neutral adducts with C- and N-nucleophiles can be isolated. Indeed, 6-nitrofuroxanopyridine **3** readily reacts with CH-acidic compounds,[6] π-excessive arenes and azoles[7] generally without added base to give stable 1,4-adducts **4**–**6** (Scheme 1). Analogous adducts were isolated upon treatment of 6-nitropyridoselenadiazole **7** with the same nucleophilic reagents under base-free conditions.[7]



1 **2**

Figure 1. Highly electrophilic 4,6-dinitrobenzofuroxan (**1**) and 5-methoxyfuroxano[3,4-*d*]pyrimidine (**2**).

Scheme 1



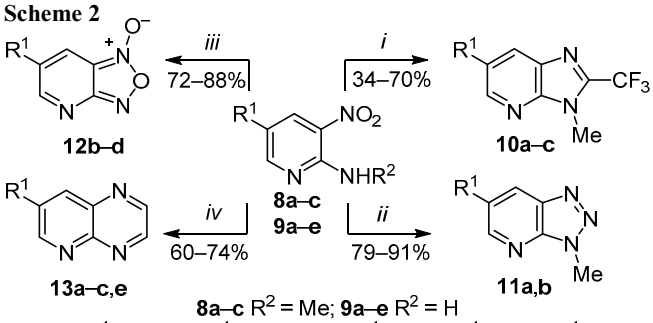
This type of adducts is of particular interest from the standpoint of design of novel pharmaceuticals since they represent highly functionalized heteroaromatics combining several pharmacophoric moieties in the same molecule (for example, furoxan and 1,4-dihydropyridine). One could expect some other condensed pyridines to be involved in the mentioned process. Therefore, in this work, we tried to figure out the influence of structural features of condensed pyridines on the addition process. We considered variations of heterocycle annulated to the pyridine ring and substituent in the pyridine cycle.

To check the influence of heterocycle annulated to nitropyridine as well as of substituent in pyridine ring, a number of azolo- and azinopyridines were selected for the synthesis (Scheme 2). Substituted 2-amino-3-nitropyridines **8** and **9** were commercially available or synthesized analogously to 5-unsubstituted derivatives (R = H).[8] Reduction of the nitro group in compounds **8a**–**c** and treatment with CF_3CO_2H resulted in the formation of imidazo[5,4-*b*]pyridines **10a**–**c** whereas nitrosation with the mixture of $NaNO_2$ and AcOH gave the corresponding triazole derivatives **11a**,**b**.

Oxidation of nitroamines **9b**–**d** with PIDA led to furoxanopyridines **12b**–**d** and, finally, reduction of the nitro group in compounds **9a**–**c**,**e** followed by condensation with glyoxal gave pyrido[2,3-*b*]pyrazines **13a**–**c**,**e**. In addition, isoxazolo[4,3-*b*]pyridine **14** was synthesized starting from commercially available 2-chloro-3,5-dinitropyridine analogously to the reported procedure (Scheme 3).[9] Target compounds **10a**, **11a**, **12b**–**d**, and **13c** were described before, while others depicted in Scheme 2 were previously unknown.

Thus, a representative set of condensed pyridines **10**–**14** was synthesized and examined in reactions with CH-acidic compounds. Imidazo- and triazolopyridines **10a**–**c** and **11a**,**b** were found to be unreactive toward dimedone, 2,4-pentanedione, and *N*,*N*'-dimethylbarbituric acid even in the presence of 1 equiv of Et_3N: in all cases starting materials were recovered. In the case of more electrophilic pyridopyrazines **13**, the substituent in pyridine ring played crucial role. Covalent 1,4-adducts **15a**–**c** were formed and isolated only with nitro derivative **13a** (Scheme 4). Dimedone and cyclohexane-1,3-dione readily reacted with no base added while acetylacetone required an equimolar amount of Et_3N added for reaction to proceed. Isoxazolopyridine **14** gave the corresponding adduct **15d** with dimedone in a base-free reaction in 79% yield. The rate of the reaction was close to that of superelectrophilic furoxanopyridine **3** thus indicating high electrophilicity of isoxazolo[4,3-*b*]pyridine system. Among furoxans **12b**–**d**, only methoxycarbonyl derivative **12b** underwent dearomative nucleophilic addition of carbon nucleophiles. Dimedone, cyclohexane-1,3-dione, and *N*,*N*'-dimethylbarbituric acid gave adducts **15e**–**g** with no added base (Scheme 4).

Scheme 2



8a–c R^2 = Me; **9a–e** R^2 = H

8–13 a R^1 = NO_2, **b** R^1 = CO_2Me, **c** R^1 = Cl, **d** R^1 = Br, **e** R^1 = CF_3

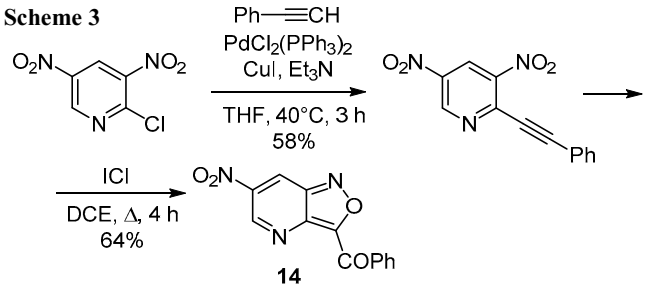
i: 1. $(NH_4)_2S$, MeOH, 20°C, 0.5 h then Δ, 0.5 h (for **8a**) or $SnCl_2$, HCl, 100°C, 1 h (for **8b**,**c**); 2. CF_3CO_2H, Δ, 24 h

ii: 1. $(NH_4)_2S$, MeOH, 20°C 0.5 h then Δ, 0.5 h (for **8a**) or $SnCl_2$,HCl, 100°C, 1 h (for **8b**,**c**); 2. $NaNO_2$, AcOH, rt, 24 h

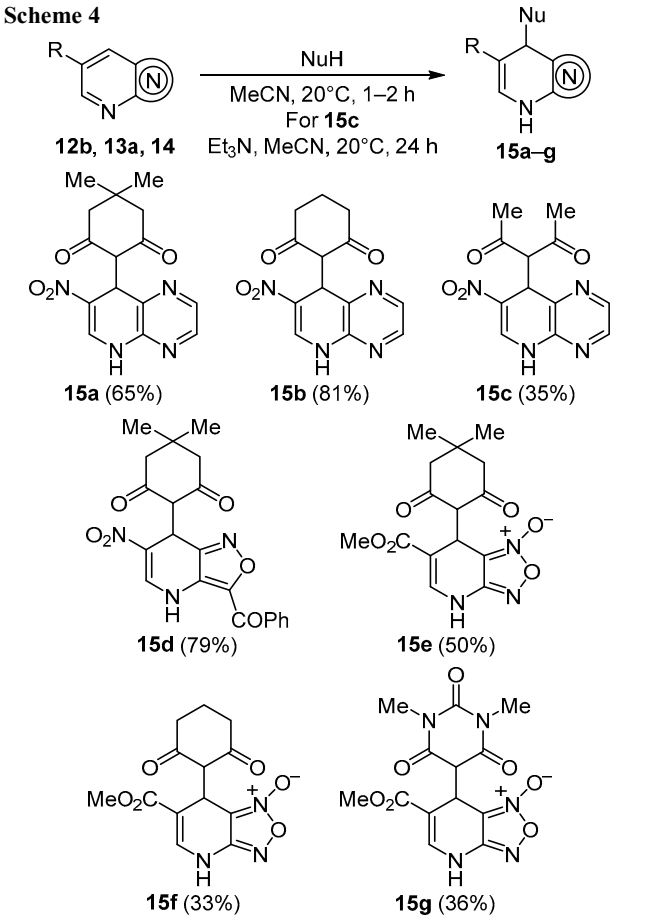
iii: $PhI(OAc)_2$, PhH, Δ, 2 h

iv: 1. $(NH_4)_2S$, MeOH, 20°C, 0.5 h then Δ, 0.5 h (for **9a**) or $SnCl_2$, HCl, 100°C, 1 h (for **9c**–**e**); 2. 40% aq glyoxal, EtOH, Δ, 3–24 h

Scheme 3



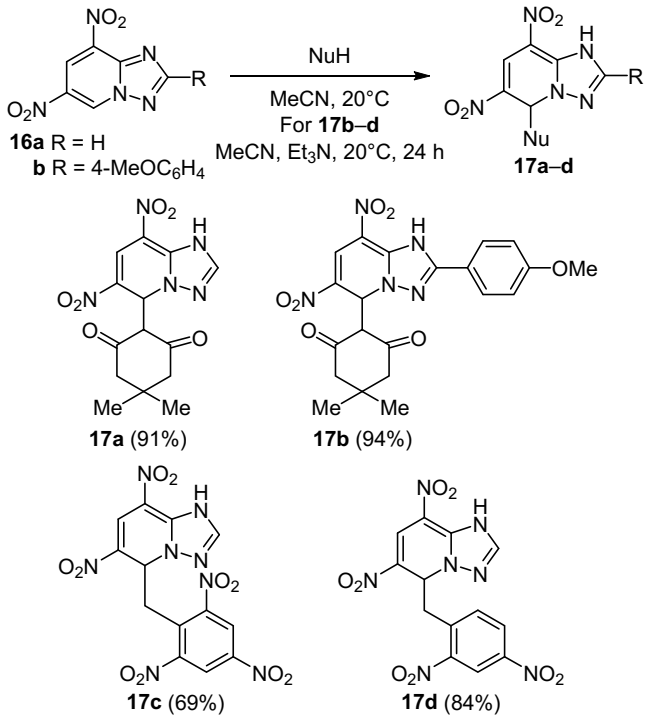
Scheme 4



All other derivatives **12** and **13** (Scheme 2) did not react with CH acids applied neither in their acidic form nor as triethylammonium salts. Unlike compounds **3** and **7**, none of the studied pyrazine and furoxan derivatives gave stable adducts with π-excessive (het)arenes (phenols, anilines, and indoles). The adduct formation was not observed or (upon addition of a base) complex mixtures were generated.

All the above-mentioned fused pyridines had the same structural features: all of them were azolo- or azino[*b*]-pyridines. However, it was of interest to check the influence of ring junction type on the reactivity of electrophiles. In this context, we examined recently described N-bridged 6,8-dinitrotriazolo[1,5-*a*]pyridines **16**[10] in reactions with selected C-nucleophiles. It turned out that dimedone readily reacts with triazolopyridine **16a**, the product precipitated shortly after mixing two reactants. At the same time, addition of 1 equiv of Et_3N was essential for reactions of triazolopyridine **16b** with dimedone and triazolopyridine **16a** with less acidic di- and trinitrotoluenes (Scheme 5).

Scheme 5



Dearomatization products **17a**–**d** were characterized by spectral methods (NMR and HRMS) as well as X-ray study for compound **17c** (Fig. 2).

The crystal structure of molecule **17c** was established by single crystal X-ray diffraction. All bond lengths and valence and torsion angles in compound **17c** are within the expected range as confirmed by Mogul geometry check;[11] the only exception is C(3)–N(3) bond (1.3809(18) Å), which is shorter than a typical C–N bond with nitro group in aromatic compounds, but the length is typical for bond adjacent to a conjugated diene system. One of the nitro groups of the trinitrotoluene fragment is apparently disordered with the refined occupancy of the minor component equal to 0.13. Due to the presence of multiple nitro substituents, a number of intramolecular contacts are found in compound **17c**, the shortest of them are O(4)···O(5) (2.864(3) Å with the major disordered component) and O(10)···C(2) (2.856(2) Å). The hydrogen atom of the triazole fragment participates in an intramolecular hydrogen bond with the oxygen atom of the adjacent nitro group (N(4)···O(1) 2.7210(15) Å, N(4)–H(4)···O(1) 107.0° with N–H set to 1.015 Å). On the other hand, the molecules in crystal are assembled into centrosymmetric H-bonded homodimers *via* two intermolecular H bonds with the same oxygen atoms of the neighboring molecules (N(4)···O(1)A 2.7634(16), N(4)–H(4)···O(1)A 161.9°) (Fig. 3). Such a dimer is found in many structures of 2-nitroanilines and related compounds,[12] and its interesting feature is additional stabilization of the motif by the direct interaction between the acceptor O atoms. In the case of molecule **17c**, due to relatively high strength of the intermolecular H bond the refined O(1)···O(1A) distance of 2.682(2) Å is significantly shorter than in the structure of 2,4,6-trinitroaniline. All other intermolecular contacts in crystal are weak and nondirectional.

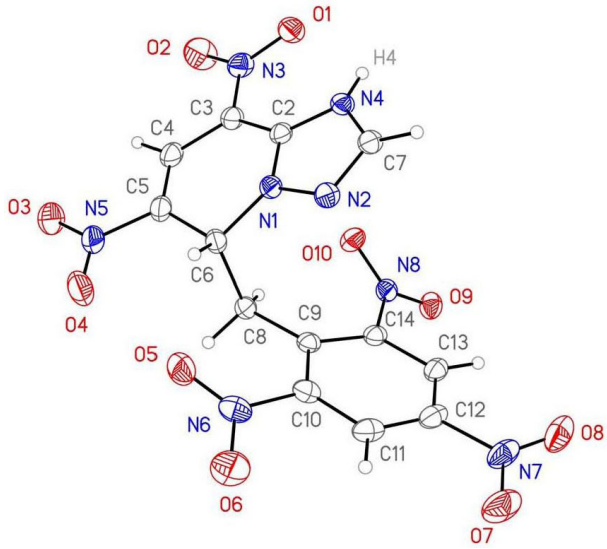


Figure 2. Molecular structure of compound **17c** with atoms represented as thermal vibration ellipsoids of 50% probability.

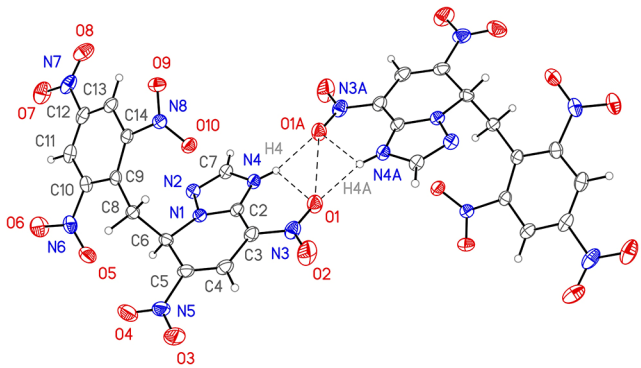
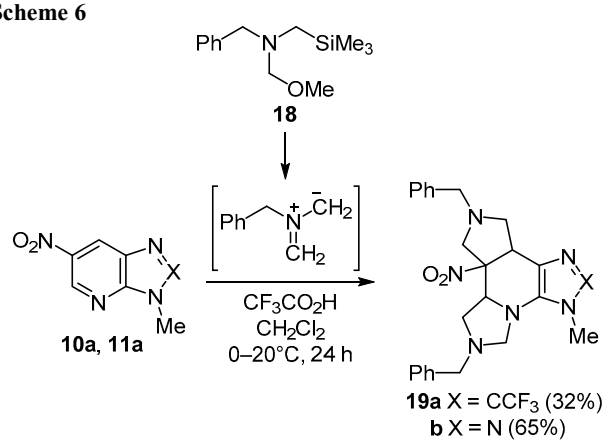


Figure 3. Centrosymmetric dimer in crystal of molecule **17c**. Non-hydrogen atoms are represented as thermal vibration ellipsoids with 50% probability, minor component of the disordered nitro group O(5)–N(6)–O(6) is omitted for clarity.

As it was mentioned above, azolopyridines **10**, **11** were unreactive toward CH-acidic compounds and their triethylammonium salts, apparently, due to insufficient π-deficiency of the annulated azole rings. At the same time, nitropyridines are known to be 2π-partners in 1,3-dipolar cycloaddition reactions with nucleophilic dipoles, such as *N*-alkylazomethine ylides.[13–15] We found that *N*-benzylazomethine ylide which was generated *in situ* from aminal **18** formed adducts of double cycloaddition with compounds **10a** and **11a** in moderate yields (Scheme 6). The resulting products **19a**,**b** consist of four different heterocycles fused together and represent previously unknown and hardly accessible heterocyclic system. It should be noted that more electrophilic azolo- and azinopyridines **12**–**14** reported in this work and forming corresponding adducts with carbon nucleophiles, in reactions with azomethine ylides generally gave complex unseparable mixture of products.

Scheme 6



All the above results together with the previously obtained data on superelectrophiles **1**–**3**, **7** allow to notice, at least at qualitative level, that in a series of structurally similar compounds, in particular, condensed pyridines, the type of reactivity depends not only on structural features (specific substituents, annulated rings) but also on some electronic factors, presumably, electrophilicity of a molecule. For example, highly electrophilic furoxan derivatives **1**, **3** readily undergo Diels–Alder reactions with nucleophilic dienes and dienophiles,[16] whereas much less electrophilic imidazo- and triazolopyridines **10**, **11** do not show such reactivity. And *vice versa*, compounds **10**, **11** gave stable adducts with azomethine ylide (Scheme 6) while superelectrophiles **1**, **3** seem to be too reactive to give sole and stable adduct. This was confirmed by our experiments: when compounds **1**, **3**, and **7** were introduced in 1,3-dipolar cycloadditions with nucleophilic dipoles, a complex mixture was obtained along with considerable tarring. The same is true for nucleophilic addition of CH acids: the more electrophilic condensed pyridine is, the more it tends to react without a base with a wider range of carbon nucleophiles .

To rationalize the reactivity of condensed pyridines in nucleophilic reactions we performed calculations of reactivity indices in the framework of DFT concept. The global electrophilicity index ω (Equation (1)) introduced by Parr et al.[17] characterizes the electrophilicity at the ground state of a molecule, i.e., in its initial geometry. This index is defined in terms of electronic potential μ and chemical hardness η and was proved to be very useful for prediction of feasibility as well as mechanisms for a significant number of polar organic reactions, including cycloadditions, nucleophilic addition, Friedel–Crafts reaction, and other electrophile/nucleophile interactions (for a review, see ref. [18]).

$$\omega = \mu^2/2\eta \quad (1)$$

In turn, μ and η can be approximately defined as functions of frontier molecular orbitals (FMO) energies: $\mu \approx 1/2(E_{HOMO} + E_{LUMO})$ and $\eta \approx E_{LUMO} - E_{HOMO}$. Values of reactivity indices calculated for the series of condensed pyridines are given in Table 1.

Based on the data provided in Table 1, a chart was built arranging the studied and related compounds in order of increasing of global electrophilicity values (Fig. 4). Except for the few deviations, it can be concluded that compounds with ω > 2.6 eV undergo 1,3-dipolar cycloaddition with azomethine ylides, however, the reactions lead to stable cycloadducts only in case of azolopyridines with ω 2.6–3.6 eV. Compounds with ω from 3.4 eV and higher do react with CH acids (with the exception of compound **11a** with ω 3.55 eV). Moreover, the higher ω value is, the wider range of CH-acidic compounds can be involved in base-free nucleophilic addition process. Finally, highly electrophilic azolopyridines, such as pyridofuroxan **3** and its benzenoid analog **1** with ω > 4.8 eV exhibit another type of reactivity – Diels–Alder reactions with nucleophilic dienes and dienophiles.[16] Similar results were obtained earlier for

Table 1. Global electrophilicity parameters* for representative condensed pyridines and related compounds

Compound	μ, eV	η, eV	ω, eV
1	–5.93	3.21	5.47
3	–5.67	3.34	4.81
7	–5.77	4.16	4.00
10a	–5.12	4.90	2.67
11a	–5.61	4.43	3.55
12b	–5.42	3.28	4.49
12c	–5.42	3.30	4.46
13a	–5.28	4.03	3.46
13b	–4.77	3.93	2.90
13c	–4.86	4.14	2.85
13e	–5.05	4.05	3.15
14	–5.73	3.42	4.79
16a	–5.73	4.35	3.78
Quinoline	–3.84	4.91	1.50
Pyridine	–3.74	6.26	1.12

* All quantities were evaluated at the B3LYP/6-31G** level of theory for the ground-state optimized geometries, using the GAUSSIAN package of programs.[19]

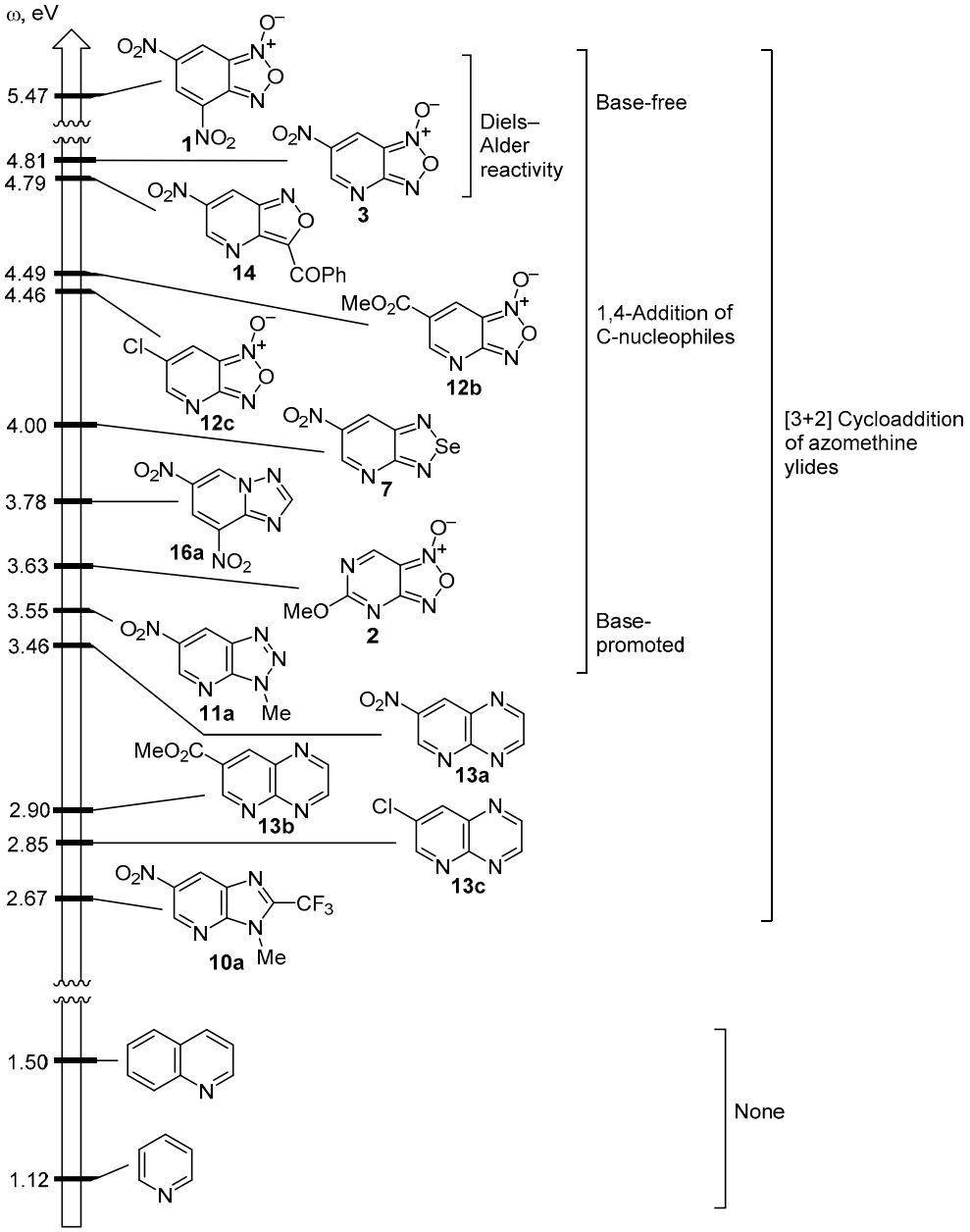


Figure 4. Relationship between global electrophilicity of π-deficient fused pyridines and some related compounds and their reactivity in nucleophilic dearomatization processes.

[3+2] and [4+2] cycloaddition reactions of nitroarenes (benzo-annulated heterocycles):[20] while less electrophilic benzazoles (ω < 2.6 eV) did not undergo 1,3-dipolar cycloaddition with azomethine ylides, their more electrophilic derivatives with ω > 2.6 eV form adducts with dipoles. The most electrophilic benzazoles such as compound **1** with ω > 5 eV are able to undergo uncatalyzed Diels–Alder reactions.[16]

As an extension of our previous work, a model series of condensed pyridines were examined in reactions with carbon nucleophiles. The study has revealed that changes in substitution pattern of the pyridine ring or in the nature of annulated heterocycle had a significant impact on the formation of adducts with CH-acidic compounds. Thus, annulation of π-deficient furoxan and pyrazine rings to pyridine core makes it possible to form covalent 1,4-adducts even under base-free conditions. The less π-deficient imidazo- and triazolopyridines were found to be unreactive toward CH acids. However, another type of nucleophilic reaction was possible, namely, 1,3-dipolar cycloaddition with azomethine ylides. Calculation of the global electrophilicity indices ω for most of the studied and related compounds allowed to generalize the relationship between structural features and particular type of reactivity of condensed pyridines.

Experimental

^{1}H NMR spectra were recorded on Bruker AM-300 spectrometer (300 MHz). ^{13}C NMR spectra were recorded on Bruker AM-300 (75 MHz), Bruker DRX-500 (126 MHz), and

Bruker Avance II 600 (151 MHz) spectrometers in DMSO-d_6 or $CDCl_3$, residual solvent peaks used as internal standard. HRMS (ESI) spectra were recorded on a Bruker micrOTOF II mass spectrometer. Melting points were measured on a Stuart SMP 20 apparatus. All reactions were monitored by TLC on ALUGRAM SIL G/UV254 plates, visualized with UV light.

All chemicals were of commercial grade and used directly without purification. Compounds **8a**–**c** and **9a**–**e** were purchased from commercial suppliers or synthesized similarly to 2-amino-3-nitropyridine and 2-methylamino-3-nitropyridine.[8]

Reduction of nitroamines 8a–c and 9a–e. Selective reduction of the 3-NO_2 group in dinitro compounds **8**, **9 a** was implemented using $(NH_4)_2S$ according to reported procedure.[21] For all other compounds, $SnCl_2$ was used as reducing agent similarly to the reported procedure.[22] Spectral characteristics of the resulting 3-amino-2-(methylamino)pyridines or 2,3-diaminopyridines coincided with those published before.

Synthesis of compounds 10a–c (General method). Solution of the corresponding 3-amino-2-(methylamino)-pyridine (4 mmol) in CF_3CO_2H (15 ml) was refluxed for 24 h, cooled to room temperature, and poured into H_2O (75 ml). The resulting mixture was neutralized with saturated $NaHCO_3$ solution, filtered, and dried on air.

3-Methyl-6-nitro-2-trifluoromethyl-3*H*-imidazo[4,5-*b*]-pyridine (10a).[23] Yield 0.69 g (70%), brown solid, mp 121–122°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.47 (1H, s, H Ar); 9.22 (1H, s, H Ar); 4.06 (3H, s, CH_3).

Methyl 3-methyl-2-trifluoromethyl-3*H*-imidazo[4,5-*b*]-pyridine-6-carboxylate (10b). Yield 0.35 g (34%), white solid, mp 118–119°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.13 (1H, s, H Ar); 8.77 (1H, s, H Ar); 4.01 (3H, s, OCH_3); 3.94 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 165.3; 150.1; 147.9; 143.0 (q, $^2J_{CF}$ = 39.0); 131.9; 130.6; 122.2; 118.5 (q, $^1J_{CF}$ = 271.8); 52.6; 30.0. Found, *m*/*z*: 260.0639 $[M+H]^+$. $C_{10}H_9F_3N_3O_2$. Calculated, *m*/*z*: 260.0641.

6-Chloro-3-methyl-2-trifluoromethyl-3*H*-imidazo[4,5-*b*]-pyridine (10c). Yield 0.57 g (61%), gray solid, mp 126–127°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.65 (1H, s, H Ar); 8.53 (1H, s, H Ar); 3.97 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 146.1; 145.6; 142.2 (q, $^2J_{CF}$ = 38.9); 133.0; 128.8; 126.5; 118.5 (q, $^1J_{CF}$ = 271.8); 29.8. Found, *m*/*z*: 236.0193 $[M+H]^+$. $C_8H_6ClF_3N_3$. Calculated, *m*/*z*: 236.0197.

Synthesis of compounds 11a,b (General method). $NaNO_2$ (1.92 g, 27.8 mmol) was added to a solution of the corresponding 3-amino-2-(methylamino)pyridine (12.6 mmol) in AcOH (40 ml) in portions at 20°C. The mixture was stirred for 24 h at room temperature, poured into H_2O (200 ml), and extracted with AcOEt (3×50 ml). Combined organic layers were dried over Na_2SO_4 and evaporated to dryness.

3-Methyl-6-nitro-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (11a). Yield 1.79 g (79%), brown solid, mp 144–146°C (151–152°C[24]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.58 (1H, s, H Ar); 9.54 (1H, s, H Ar); 4.40 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 148.7; 147.4; 142.6; 136.1; 126.9; 34.6. Found, *m*/*z*: 180.0519 $[M+H]^+$. $C_6H_6N_5O_2$. Calculated, *m*/*z*: 180.0516.

Methyl 3-methyl-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine-6-carboxylate (11b). Yield 2.23 g (91%), brown solid, mp 157–158°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.25 (1H, s, H Ar); 9.05 (1H, s, H Ar); 4.34 (3H, s, OCH_3); 3.95 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 165.0; 151.1; 147.5; 135.6; 130.4; 122.2; 52.8; 33.2. Found, *m*/*z*: 193.0717 $[M+H]^+$. $C_8H_9N_4O_2$. Calculated, *m*/*z*: 193.0720.

Synthesis of compounds 12b–d (General method). $PhI(OAc)_2$ (1.93 g, 6 mmol) was added to a suspension of compound **9b**–**d** (4.6 mmol) in PhH (40 ml). The mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and the residue was washed thoroughly with hexane and dried on air.

Methyl [1,2,5]oxadiazolo[3,4-*b*]pyridine-6-carboxylate 1-oxide (12b). Yield 0.79 g (88%), yellow solid, mp 104–106°C (mp 106.5–107.5°C[25]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.21 (1H, br. s, H Ar); 8.69 (1H, br. s, H Ar); 3.94 (3H, s, OCH_3). Found, *m*/*z*: 196.0348 $[M+H]^+$. $C_7H_6N_3O_4$. Calculated, *m*/*z*: 196.0353.

6-Chloro-[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (12c).[26] Yield 0.61 g (77%), brown solid, mp 128–129°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.87 (1H, br. s, H Ar); 8.55 (1H, br. s, H Ar).

6-Bromo-[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-oxide (12d). Yield 0.72 g (72%), brown solid, mp 206–207°C (mp 208–210°C[27]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.92 (1H, br. s, H Ar); 8.70 (1H, br. s, H Ar).

Synthesis of compounds 13a–c,e (General method). A solution of the corresponding 2,3-diaminopyridine (6.5 mmol) and 40% aqueous glyoxal (0.9 ml, 7.8 mmol) in EtOH (40 ml) was heated under reflux for 3 h (24 h for compound **13a**), cooled to 0°C. The precipitate was filtered off, washed with cold EtOH, and dried on air.

7-Nitropyrido[2,3-*b*]pyrazine (13a). Yield 0.68 g (60%), brown solid, mp 195–196°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.86 (1H, s, H Ar); 9.37 (2H, s, H Ar); 9.30 (1H, s, H Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 152.6; 151.3; 149.1; 147.7; 143.6; 135.9; 134.4. Found, *m*/*z*: 177.0408 $[M+H]^+$. $C_7H_4N_4O_2$. Calculated, *m*/*z*: 177.0407.

Methyl pyrido[2,3-*b*]pyrazine-7-carboxylate (13b). Yield 0.90 g (74%), white solid, mp 180–181°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.56 (1H, d, *J* = 2.0, H Ar); 9.26 (1H, s, H Ar); 9.19 (1H, s, H Ar); 8.96 (1H, d, *J* = 2.0, H Ar); 3.99 (3H, s, OCH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 164.4; 153.0; 152.5; 150.5; 148.3; 140.0; 136.5; 126.8; 53.0. Found, *m*/*z*: 190.0616 $[M+H]^+$. $C_9H_8N_3O_2$. Calculated, *m*/*z*: 190.0611.

7-Chloropyrido[2,3-*b*]pyrazine (13c). Yield 0.88 g (81%), light-brown solid, mp 158–160°C (mp 159–160.5°C[28]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.20 (1H, d, *J* = 2.4, H Ar); 9.17 (1H, s, H Ar); 9.11 (1H, s, H Ar); 8.78 (1H, d, *J* = 2.4, H Ar). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 153.2; 149.1; 148.8; 147.9; 137.6; 136.7; 131.5. Found, *m*/*z*: 166.0167 $[M+H]^+$. $C_7H_5ClN_3$. Calculated, *m*/*z*: 166.0162.

7-(Trifluoromethyl)pyrido[2,3-*b*]pyrazine (13e). Yield 0.77 g (60%), white solid, mp 149–150°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.50 (1H, d, *J* = 2.0, H Ar); 9.31 (1H, s, H Ar); 9.22 (1H, s, H Ar); 9.05 (1H, d, *J* = 2.0, H Ar). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 152.1; 150.9; 149.5 (d, $^3J_{CF}$ = 3.7); 148.6; 137.2 (d, $^3J_{CF}$ = 3.7); 136.0; 126.2 (q, $^2J_{CF}$ = 33.0); 123.1 (q, $^1J_{CF}$ = 273.1). Found, *m*/*z*: 200.0431 $[M+H]^+$. $C_8H_4F_3N_3$. Calculated, *m*/*z*: 200.0430.

(6-Nitroisoxazolo[4,3-*b*]pyridin-3-yl)(phenyl)methanone (14). A mixture of 2-chloro-3,5-dinitropyridine (1.02 g, 5 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), and Et_3N (1.4 ml, 10 mmol) was suspended in anhydrous THF (10 ml) under inert atmosphere. Phenylacetylene (0.62 ml, 5.5 mmol) was then added followed by addition of CuI (2.5 mol %). The reaction mixture was stirred under argon at 40°C for 3 h, evaporated under reduced pressure, and the residue was purified by column chromatography ($CHCl_3$) to give 0.78 g (58%) of (3,5-dinitropyridin-2-yl)phenylacetylene which was used directly in the next step. The above compound (0.27g, 1 mmol) was dissolved in anhydrous 1,2-dichloroethane (20 ml), and iodine monochloride (3 mol %) was added. The mixture was stirred under reflux for 4 h, cooled to room temperature, washed with sat. aqueous $Na_2S_2O_3$ and H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column chromatography, eluent $CHCl_3$. Yield 0.17 g (64%), beige solid, mp 135–137°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 9.55 (1H, d, *J* = 2.2, H Ar); 9.08 (1H, d, *J* = 2.2, H Ar); 8.23 (2H, d, *J* = 7.4, H Ph); 7.77 (1H, t, *J* = 7.4, H Ph); 7.63 (2H, t, *J* = 7.7, H Ph). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 181.1; 163.0; 150.4; 149.6; 144.7; 135.9; 135.7; 134.9; 131.2; 129.7; 122.7. Found, *m*/*z*: 270.0508 $[M+H]^+$. $C_{13}H_7N_3O_4$. Calculated, *m*/*z*: 270.0509.

Synthesis of compounds 15a–g (General method). Corresponding nucleophile (dimedone, cyclohexane-1,3-dione, or *N*,*N*'-dimethylbarbituric acid) (1 mmol) was added to a solution of compound **12b**, **13a**, or **14** (1 mmol) in MeCN (10 ml). The reaction mixture was stirred at 20°C for 1–2 h (monitored by TLC), the precipitated product was filtered off, washed with MeCN, and dried on air. In case of compound **15c**, Et_3N (0.14 ml, 1 mmol) was added to the reaction mixture, the reaction mixture was stirred for 24 h, poured into H_2O (50 ml), acidified with concd HCl to pH 3, filtered, and dried. ^{1}H and ^{13}C NMR spectra of compounds **15a**–**g** in some cases contain double set of signals corresponding to the enol and dioxo forms of the product. Due to the tautomerism of these two forms some signals appeared as broad singlets.

5,5-Dimethyl-2-(7-nitro-5,8-dihydropyrido[2,3-*b*]pyrazin-8-yl)cyclohexane-1,3-dione (15a). Yield 0.206 g (65%), yellow solid, mp 185–186°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 10.83 (1H, br. s, OH); 10.62 (1H, d, *J* = 6.5, NH); 8.09 (1H, s, H Ar); 8.03 (1H, s, H Ar); 8.00 (1H, d, *J* = 6.5, CH); 5.74 (1H, s, CH); 2.21 (4H, br. s, $2CH_2$); 0.91 (6H, s, $2CH_3$). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 194.5; 170.9; 145.3; 143.9; 140.2; 138.9; 136.8; 125.8; 116.8; 102.4; 34.8; 31.7; 27.6. Found, *m*/*z*: 317.1240 $[M+H]^+$. $C_{15}H_{17}N_4O_4$. Calculated, *m*/*z*: 317.1244.

2-(7-Nitro-5,8-dihydropyrido[2,3-*b*]pyrazin-8-yl)cyclohexane-1,3-dione (15b), enolic form. Yield 0.232 g (81%), light-yellow solid, mp 191–192°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 10.94 (1H, s, OH); 10.63 (1H, d, *J* = 4.7, NH); 8.08 (1H, s, H Ar); 8.02 (1H, s, H Ar); 7.98 (1H, d, *J* = 5.4, CH); 5.74 (1H, s, CH); 2.26 (4H, br. s, $2CH_2$); 1.72 (2H, br. s, CH_2). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 151.2; 149.2; 146.5; 145.0; 141.4; 140.2; 138.0; 126.9; 119.0; 36.1; 30.4; 21.5. Found, *m*/*z*: 289.0931 $[M+H]^+$. $C_{13}H_{13}N_4O_4$. Calculated, *m*/*z*: 289.0931.

3-(7-Nitro-5,8-dihydropyrido[2,3-*b*]pyrazin-8-yl)pentane-2,4-dione (15c), mixture of enolic and dioxo forms in a ratio of about 1:3. Yield 0.096 g (35%), brown solid, mp 182–183°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major tautomer: 8.40 (1H, s, NH); 7.93 (1H, s, H Ar); 7.90 (1H, s, H Ar); 7.44 (1H, s, CH); 5.94 (1H, s, CH); 4.82 (1H, s, CH); 2.28 (3H, s, CH_3); 2.17 (3H, s, CH_3); minor tautomer: 9.02 (1H, s, NH); 8.31 (1H, s, H Ar); 7.55 (1H, s, CH); 6.47 (1H, s, CH); 5.86 (1H, s, CH); 4.49 (1H, s , CH); other signals overlap with a major tautomer signals. ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 194.2; 194.0; 169.1; 168.5; 152.1; 148.6; 138.9; 138.1; 136.5; 134.3; 129.4; 124.2; 118.6; 117.6; 111.9; 110.7; 89.0; 88.8; 55.2; 53.0; 30.5; 30.3; 16.3. Found, *m*/*z*: 277.0932 $[M+H]^+$. $C_{12}H_{13}N_4O_4$. Calculated, *m*/*z*: 277.0931.

5,5-Dimethyl-2-[6-nitro-3-(phenylcarbonyl)-4,7-dihydroisoxazolo[4,3-*b*]pyridin-7-yl]cyclohexane-1,3-dione (15d). Yield 0.320 g (79%), yellow solid, mp 244–246°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 11.18 (1H, br. s, OH); 10.56 (1H, d, *J* = 6.1, NH); 8.13 (2H, d, *J* = 7.7, H Ph); 8.01 (1H, d, *J* = 4.3, CH); 7.75 (1H, t, *J* = 7.3, H Ph); 7.64 (2H, t, *J* = 7.5, H Ph); 5.75 (1H, br. s, CH); 2.27 (4H, br. s, $2CH_2$); 0.93 (6H, s, $2CH_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 181.9; 173.1; 172.6; 158.6; 147.4; 138.6; 136.3; 135.3; 130.5; 130.2; 127.9; 50.9; 43.7; 32.9; 29.0; 28.5. Found, *m*/*z*: 410.1340 $[M+H]^+$. $C_{21}H_{20}N_3O_6$. Calculated, *m*/*z*: 410.1347.

Methyl 7-(4,4-dimethyl-2,6-dioxocyclohexyl)-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine-6-carboxylate 1-oxide (15e). Yield 0.170 g (50%), brown solid, mp 125–126°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 10.45 and 10.38 (1H, both d, *J* = 5.5, NH of diketo and enol forms); 7.32 (1H, d, *J* = 5.5, CH); 5.36 and 5.11 (1H, both s, CH); 3.52 (3H, s, OCH_3), 2.20 (4H, br. s, $2CH_2$); 0.94 and 0.93 (6H, both s, $2CH_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 165.6; 152.5; 136.2; 108.3; 59.8; 50.9; 31.6; 30.7; 27.6; 24.8; 20.8; 14.1. Found, *m*/*z*: 336.1188 $[M+H]^+$. $C_{15}H_{18}N_3O_6$. Calculated, *m*/*z*: 336.1190.

Methyl 7-(2,6-dioxocyclohexyl)-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine-6-carboxylate 1-oxide (15f). Yield 0.100 g (33%), brown solid, mp 144–146°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 11.07 (1H, br. s, OH); 10.43 (1H, d, *J* = 5.2, NH); 7.30 (1H, d, *J* = 5.2, CH); 5.12 (1H, s, CH); 3.52 (3H, s, OCH_3); 2.28 (4H, br. s, $2CH_2$); 1.78–1.72 (2H, m, CH_2). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 200.4; 166.0; 152.9; 137.6; 136.5; 131.1; 111.6; 108.6; 102.6; 60.2; 51.2; 25.6; 21.2; 20.9; 16.6; 14.5. Found, *m*/*z*: 308.0878 $[M+H]^+$. $C_{13}H_{14}N_3O_6$. Calculated, *m*/*z*: 308.0877.

Methyl 7-(1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)-4,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyridine-6-carboxylate 1-oxide (15g). Yield 0.126 g (36%), white solid, mp 189–190°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 10.87 (1H, d, *J* = 5.3, NH); 7.51 (1H, s, CH); 4.79 (1H, s, CH); 3.55 (3H, s, OCH_3); 3.14 (3H, s, CH_3); 3.06 (3H, s, CH_3). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 165.8; 164.1; 159.6; 150.0; 149.5; 136.0; 135.9; 128.9; 97.6; 54.1; 53.4; 51.7; 29.2; 28.8; 28.1. Found, *m*/*z*: 352.0883 $[M+H]^+$. $C_{13}H_{14}N_5O_7$. Calculated, *m*/*z*: 352.0888.

Synthesis of compounds 17a–d (General method). Triazolo[1,5-*a*]pyridine **16a**,**b**[10] (1 mmol) and nucleophile (1.1 mmol) were dissolved in MeCN (10 ml). Compound **17a** precipitated in few minutes and was filtered off, washed with MeCN, and dried on air. In case of adducts **17b**–**d**, Et_3N (0.14 ml, 1 mmol) was added and the mixture was stirred for 24 h, poured into H_2O (50 ml), and acidified with concd HCl to pH 2. The precipitated products were filtered off, washed with H_2O, and dried.

2-(6,8-Dinitro-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridin-5-yl)-5,5-dimethylcyclohexane-1,3-dione (17a). Yield 0.33 g (91%), yellow solid, mp 226–227°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.76 (1H, s, H Ar); 8.41 (1H, s, H Ar); 6.92 (1H, s, CH); 2.21 (4H, br. s, $2CH_2$); 0.91 (6H, s, $2CH_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 143.0; 141.5; 141.3; 127.3; 127.2; 106.9; 52.7; 49.2; 31.7; 27.7; 27.5. Found, *m*/*z*: 350.1086 $[M+H]^+$. $C_{14}H_{16}N_5O_6$. Calculated, *m*/*z*: 350.1095.

2-[2-(4-Methoxyphenyl)-6,8-dinitro-1,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridin-5-yl]-5,5-dimethylcyclohexane-1,3-dione (17b). Yield 0.44 g (94%), yellow solid, mp 205–207°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.45 (1H, s, H Ar); 7.98 (2H, d, *J* = 8.7, H Ar); 7.09 (2H, d, *J* = 8.7, H Ar); 6.94 (1H, s, CH); 3.83 (3H, s, OCH_3); 2.23 (4H, br. s, $2CH_2$); 0.92 (6H, s, $2CH_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 161.8; 151.5; 144.5; 129.3; 127.4; 127.0; 116.5; 114.4; 107.1; 55.5; 52.8; 46.4; 31.9; 28.0; 27.5. Found, *m*/*z*: 456.1501 $[M+H]^+$. $C_{21}H_{22}N_5O_7$. Calculated, *m*/*z*: 456.1514.

6,8-Dinitro-5-(2,4,6-trinitrobenzyl)-1,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridine (17c). Yield 0.31 g (69%), brown solid, mp 162–163°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.07 (2H, s, H Ar); 8.66 (1H, s, H Ar); 8.47 (1H, s, H Ar); 6.34 (1H, dd, *J* = 7.9, *J* = 6.0, CH); 3.76 (1H, dd, *J* = 14.3, *J* = 6.0, CH_2); 3.55 (1H, dd, *J* = 14.3, *J* = 8.2, CH_2). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 150.9; 146.7; 143.0; 142.6; 130.2; 128.3; 124.6; 123.0; 107.2; 58.0; 32.2. Found, *m*/*z*: 437.0435 $[M+H]^+$. $C_{13}H_9N_8O_{10}$. Calculated, *m*/*z*: 437.0436.

5-(2,4-Dinitrobenzyl)-6,8-dinitro-1,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridine (17d). Yield 0.33 g (84%), orange solid, mp 210–211°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.78 (1H, s, H Ar); 8.69 (1H, s, H Ar); 8.44–8.39 (2H, m, H Ar); 7.56 (1H, d, *J* = 8.3, H Ar); 6.35 (1H, br. s, CH); 3.75–3.58 (2H, m, CH_2). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 149.4; 146.7; 142.8; 142.5; 137.3; 134.8; 128.4; 127.2; 124.4; 120.0; 107.0; 58.8; 36.3. Found, *m*/*z*: 392.0580 $[M+H]^+$. $C_{13}H_{10}N_7O_8$. Calculated, *m*/*z*: 392.0585.

Synthesis of compounds 19a,b (General method). 0.1 M solution of CF_3CO_2H in CH_2Cl_2 (1 ml) was added to an ice-cold solution of compound **10a** or **11a** (1 mmol) and amine **18**[29] (1.04 ml, 4 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 24 h at 20°C, washed with saturated $NaHCO_3$ solution, and the solvent was removed under reduced pressure. The residue was purified by column chromatography, eluent $CHCl_3$.

6,9-Dibenzyl-3-methyl-7b-nitro-2-(trifluoromethyl)-3,5,6,7,7a,7b,8,9,10,10a-decahydrodiimidazo[1,5-*a*:4',5'-*e*]-pyrrolo[3,4-*c*]pyridine (19a). Yield 0.162 g (32%), light-yellow solid, mp 141–142°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.30–7.26 (10H, m, H Ph); 4.04 (1H, br. s, CH); 3.98 (1H, d, *J* = 5.7, CH); 3.84–3.78 (3H, m, CH, CH_2); 3.63–3.57 (5H, m, CH, NCH_3); 3.39 (2H, dd, *J* = 15.3, *J* = 10.1, CH_2); 3.13 (1H, t, *J* = 9.4, CH); 3.03 (2H, dd, *J* = 9.0, *J* = 6.5, CH_2); 2.91 (1H, d, *J* = 10.4, CH); 2.81 (2H, dd, *J* = 8.6, *J* = 5.9, CH_2). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 137.6; 135.6; 130.1 (q, $^2J_{CF}$ = 39.3); 128.7; 128.5; 128.3; 127.5; 122.9; 119.2 (q, $^1J_{CF}$ = 268.6); 91.2; 71.7; 64.6; 60.0; 59.2; 58.6; 57.7; 52.8; 41.3; 30.7. Found, *m*/*z*: 513.2219 $[M+H]^+$. $C_{26}H_{28}F_3N_6O_2$. Calculated, *m*/*z*: 513.2220.

6,9-Dibenzyl-3-methyl-7b-nitro-3,5,6,7,7a,7b,8,9,10,10a-decahydroimidazo[1,5-*a*]pyrrolo[3,4-*c*][1,2,3]triazolo-[4,5-*e*]pyridine (19b). Yield 0.29 g (65%), brown solid, mp 137–139°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.43–7.20 (10H, m, H Ph); 4.06–3.96 (5H, m, CH, CH_2); 3.88 (3H, s, NCH_3); 3.83–3.59 (4H, m, CH_2); 3.49 (1H, d, *J* = 10.6, CH); 3.25 (2H, t, *J* = 9.0, CH_2); 3.08–2.98 (1H, m, CH); 2.90–2.81 (2H, m, CH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 138.0; 137.5; 137.4; 130.4; 128.6; 128.3; 127.6; 127.5; 90.1; 70.9; 64.2; 59.5; 59.2; 58.5; 57.7; 52.8; 40.1; 33.9. Found, *m*/*z*: 446.2298 $[M+H]^+$. $C_{24}H_{28}N_7O_2$. Calculated, *m*/*z*: 446.2299.

X-ray diffraction data of compound 17c were collected on a Bruker APEX DUO diffractometer (λ(MoKα) 0.71073 Å, 2θ < 61.10°). Red crystals, obtained by the slow evaporation of the solution of compound **17c** in Me_2CO, of $C_{13}H_8N_8O_{10}$ at 120(2) K are monoclinic, space group $P2_1/c$; *a* 13.4033(6), *b* 10.3227(5), *c* 12.1255(5) Å; β 103.4020 (10)°; *V* 1631.98(13) Å^3; *Z* 4 (*Z*' 1); d_{calc} 1.776 g·cm^{-3}. Intensities of 5003 independent reflections (R_{int} 0.0303) out of 29504 collected were used in structure solution and refinement. The structure was solved by the dual-space method with SHELXT program[30] and refined by the full-matrix least-squares technique against F^2 in the anisotropic approximation with SHELXL program.[31] The hydrogen atom connected to the nitrogen atom was found from the difference Fourier synthesis and refined isotropically. Other hydrogen atoms were placed in calculated positions and refined in the riding model with U_{iso}(H) equal to $1.2U_{eq}$(C) of the connected carbon atoms. The refinement converged to R10.0430 (calculated for 4027 observed reflections with $I > 2\sigma(I)$), wR_2 0.1141 and *GOF* 1.013. Full crystallographic data is deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1943950).

Global electrophilicity parameters calculations. Geometry optimization of isolated molecules was carried

out at the B3LYP/6-31G** level of theory. The GAUSSIAN program was used for calculation.[19]

Supplementary information file containing ^{1}H, ^{13}C NMR spectra and HRMS analyses of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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