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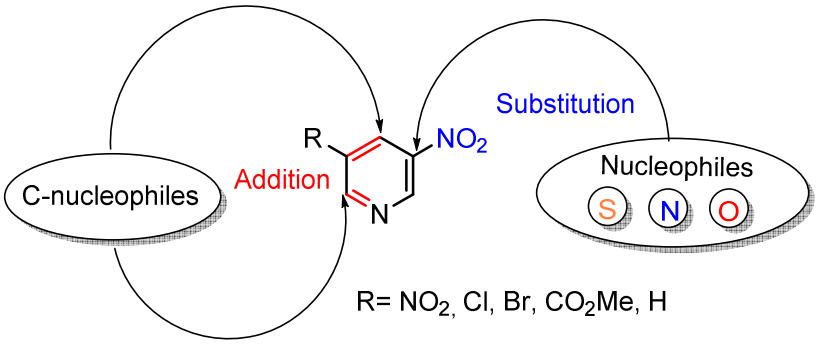
Graphical Abstract



Reactions of 3-R-5-nitropyridines with nucleophiles: nucleophilic substitution *vs* conjugate addition.

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Abstract:

A number of 3-R-5-nitropyridines were synthesized and their reactions with various types of nucleophiles were investigated. The reaction outcome depends on the nature of a nucleophile: in case of anionic O-, N- and S-nucleophiles the previously unreported substitution of non-activated nitro group occurred while carbon nucleophiles underwent dearomatization of the pyridine ring with the formation of products of 1,2- and 1,4-addition.

Keywords: nitro group, nitropyridines, nucleophilic substitution, dihydropyridines, oxidative nucleophilic substitution, nucleophilic addition.

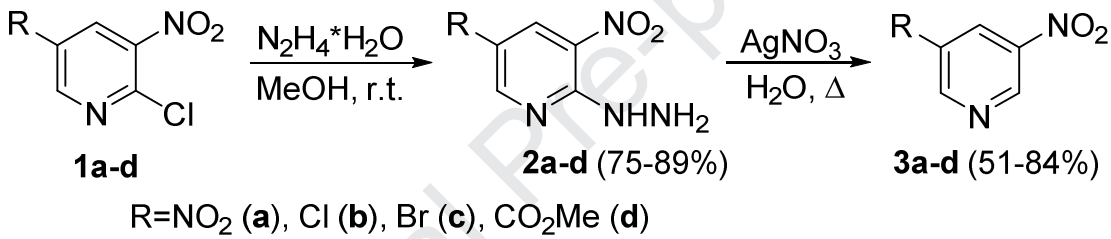
Introduction

Nitropyridines represent an important class of organic compounds that are used in the synthesis of biologically active compounds [1] possessing antitumor [2,3] or anti-HIV activity [4-6]. Other applications of nitropyridines include herbicides [7], pesticides [8], energetic compounds [9] and highly efficient organic optical materials [10]. Due to numerous useful properties, there is a challenge to develop methods for the synthesis of new functionalized nitropyridine derivatives. At the same time the number of general approaches for the functionalization of nitropyridines is quite limited. For example, nucleophilic aromatic substitution is one of the most popular ways to functionalize nitro (het)arenes [11-15]. The nitro group is considered as one of the best activating groups as well as good leaving group which can be replaced under the action of nucleophiles of different nature. However, nucleophilic substitution of non-activated nitro groups is rare and described mostly in polynitrobenzene series [16-20]. For nitropyridines containing non-activated nitro groups, such reactions have not been studied before. Only one example of the substitution of a nitro group in 3,5-dinitropyridine is known so far [21].

This work is a part of our ongoing research on the chemistry of nitropyridines. Earlier, we have developed efficient methods for the annulations of different heterocyclic rings to nitropyridine core. As a result, a number of new derivatives of decahydrodipyrrolo[3,4-b:3',4'-d]pyridine [22-23], pyrido[3,2-*b*][1,4]benzoxazine [24], 1,4-dihydropyridine fused with furoxan or selenadiazole [25-26] and [1,2,4]triazolo[1,5-a]pyridine [27] were synthesized. Herein we report on reactions of 3-R-5-nitropyridines with nucleophilic reagents.

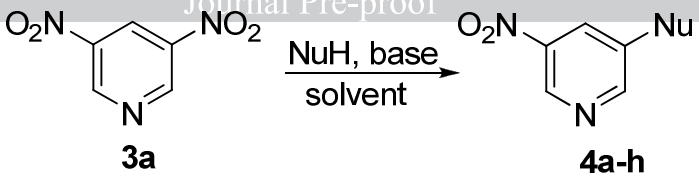
Results and discussion.

The starting substituted 5-nitropyridines were synthesized according to the scheme 1. The chlorine atom in commercially available compounds **1a-d** is readily substituted under the action of hydrazine hydrate. Next, pyridines **2** were oxidized in the presence of silver nitrate to give target 3-R-5-nitropyridines in good yields.



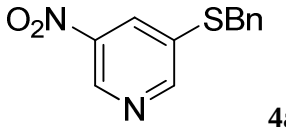
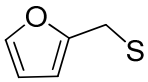
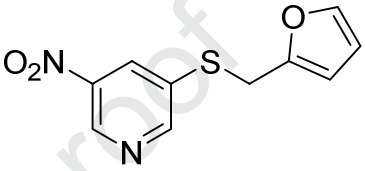
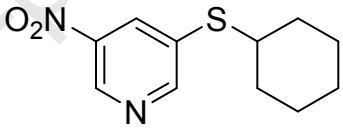
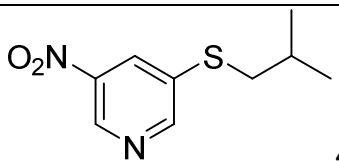
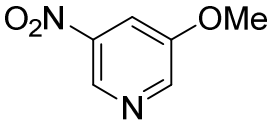
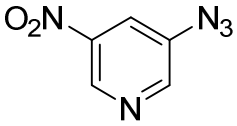
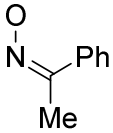
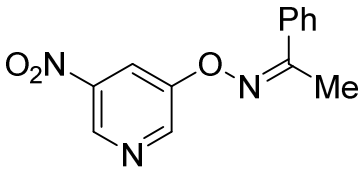
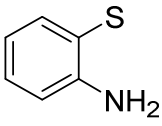
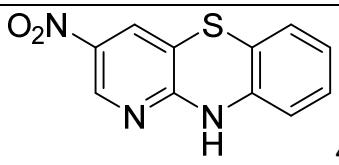
Scheme 1. Synthesis of 3-R-5-nitropyridines **3a-d**

3,5-Dinitropyridine **3a** was selected as a model compound to study the reactions with number of anionic nucleophiles. Interaction of **3a** with equimolar amounts of the corresponding alkanethiols in the presence of K_2CO_3 resulted in substitution of one of the nitro groups to give 3-alkylthio-5-nitropyridines **4a-d**, scheme 2, table 1 (entries 1-4). Using the excess of nucleophilic reagent at the same temperature or under more drastic conditions did not affect the reaction outcome: the substitution of the second nitro group was not observed. Similarly, reactions of **3a** with NaN_3 in DMF at 100°C or MeONa in boiling MeOH led to the products of displacement of the nitro group **4e** and **4f** respectively (table 1, entries 5 and 6). We have also found that the nitro group in compound **3a** can be replaced under the action of acetophenone oxime salt giving rise to pyridine **4g**, table 1, entry 7. Interestingly, when 2-aminothiophenol was taken as a nucleophilic reagent, the substitution product underwent *in situ* cyclization, apparently, via oxidative nucleophilic substitution of hydrogen in position 2. Compound **4h** showed spectral characteristics similar to those described previously [13].



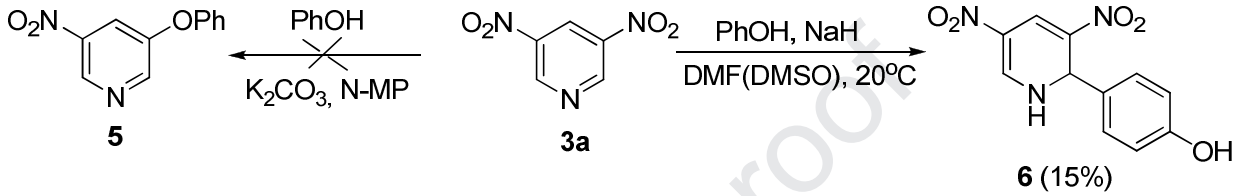
Scheme 2. Nucleophilic substitution of non-activated nitro group in 3,5-dinitropyridine

Table 1. Reaction conditions and isolated yields of compounds **4a-h**

Entry	Nu	Reaction conditions	Product	Yield, %
1	BnS	K_2CO_3, N-MP, 50°C, 4h	 **4a**	34
2		K_2CO_3, N-MP, 50°C, 4h	 **4b**	36
3	cyclo-$C_6H_{11}S$	K_2CO_3, N-MP, 50°C, 4h	 **4c**	59
4	i-BuS	K_2CO_3, N-MP, 50°C, 4h	 **4d**	48
5	MeO	MeONa, MeOH, 65°C, 24h	 **4e**	30
6	N_3	DMF, 100°C, 3h	 **4f**	48
7		NaH, DMF, 20°C, 24h	 **4g**	67
8		K_2CO_3, N-MP, 50°C, 4h	 **4h**	85

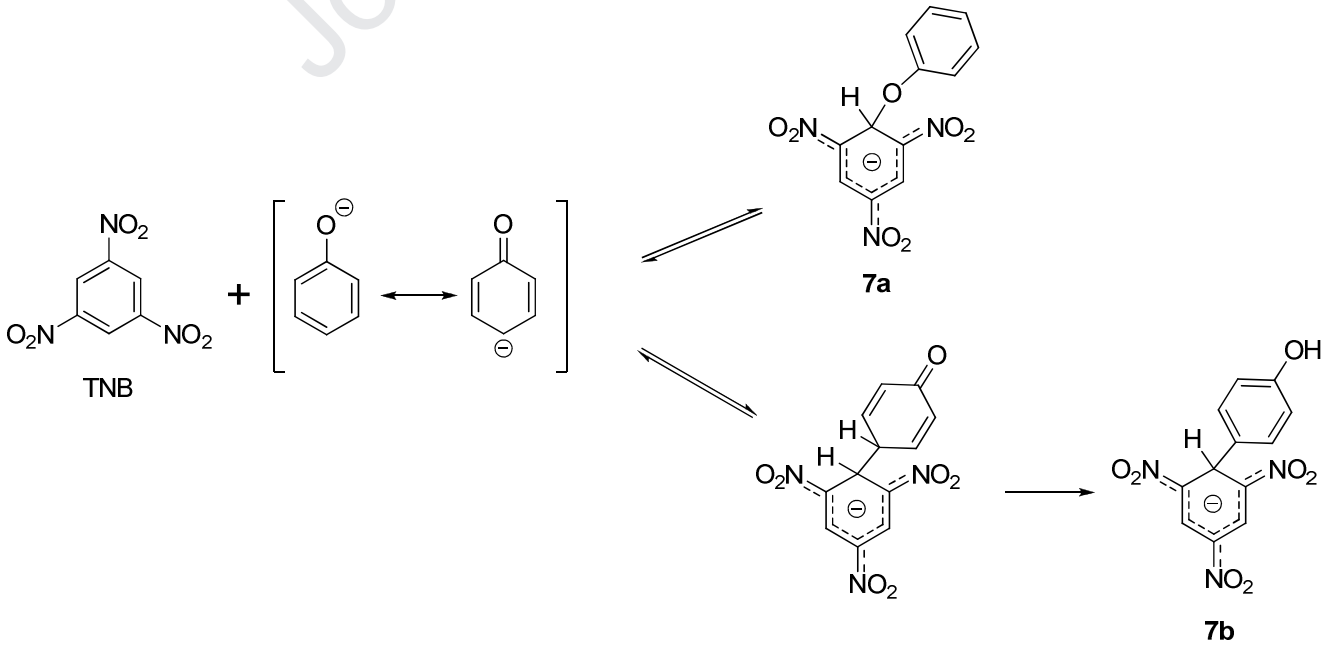
It is known that the nitro group in 1,3,5-trinitrobenzene (TNB) is readily substituted under the action of various S-, N-, O-nucleophiles in aprotic dipolar solvents (N-MP, DMF) at 50-100°C [22-26]. Compounds **4a-h** were obtained in moderate to good yields under almost similar conditions. However, evaluation of the reaction temperature resulted in considerable tarring. These results indicate that the nitrogen atom of the pyridine ring has an activating effect close to that of NO_2.

Our attempts to substitute the nitro group in **3a** with OPh group failed. Application of standard conditions (PhOH, K_2CO_3, N-MP, 50-100°C) led solely to significant resinification; formation of compound **5** was not observed. Surprisingly, reaction with phenol in the presence of sodium hydride in DMF or DMSO gave the dearomatization product **6**, scheme 3.



Scheme 3. Interaction of 3,5-dinitropyridine **3a** with phenol.

In this case the reaction pattern changed apparently due to ambidency of phenoxide ion: it can act either as an oxygen or as a carbon nucleophile. The interaction of TNB with phenoxide ion was studied using NMR monitoring of the reaction mixture [28,29]. It was found that anionic adduct **7a** was initially formed, which then gradually converted to thermodynamically more stable complex **7b**. In addition, the authors noted that on acidifying of solutions of **7a**, TNB was recovered. Unlike **7a**, acidification of complex **7b** did not lead to its destruction.



Scheme 4. Ambidency of phenoxide ion in reaction with TNB

It should be noted that nucleophilic dearomatization of the pyridine nucleus usually requires activation to proceed since pyridine itself is not electrophilic enough. The quaternization of nitrogen atom is generally employed to prepare pyridinium salts that display enhanced electrophilic character [30,31]. At the same time the direct dearomatization of pyridines is a significant challenge in modern organic chemistry. Direct addition of phenol to pyridine ring is the first example of such process in the case of nitropyridine derivatives.

The structure of compound **6** was confirmed by spectral methods, as well as X-ray diffraction data. The molecule **6** crystallizes with a solvate water molecule (Fig 1).

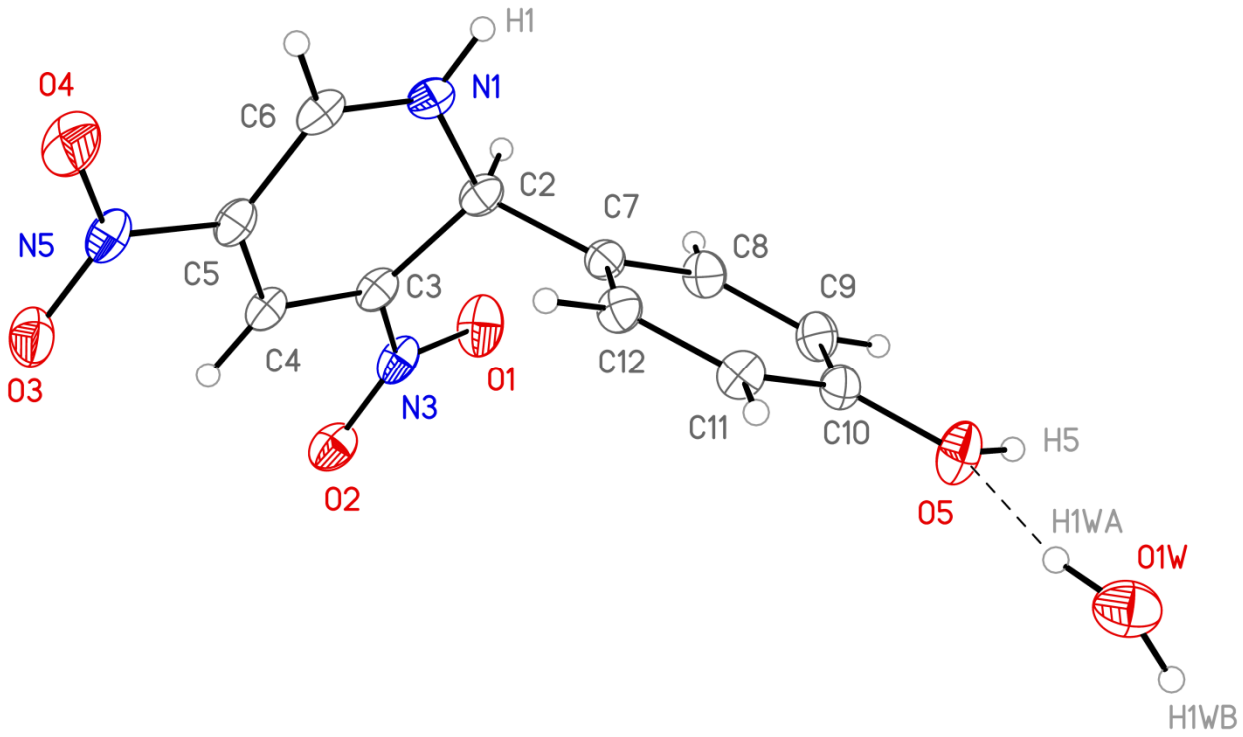
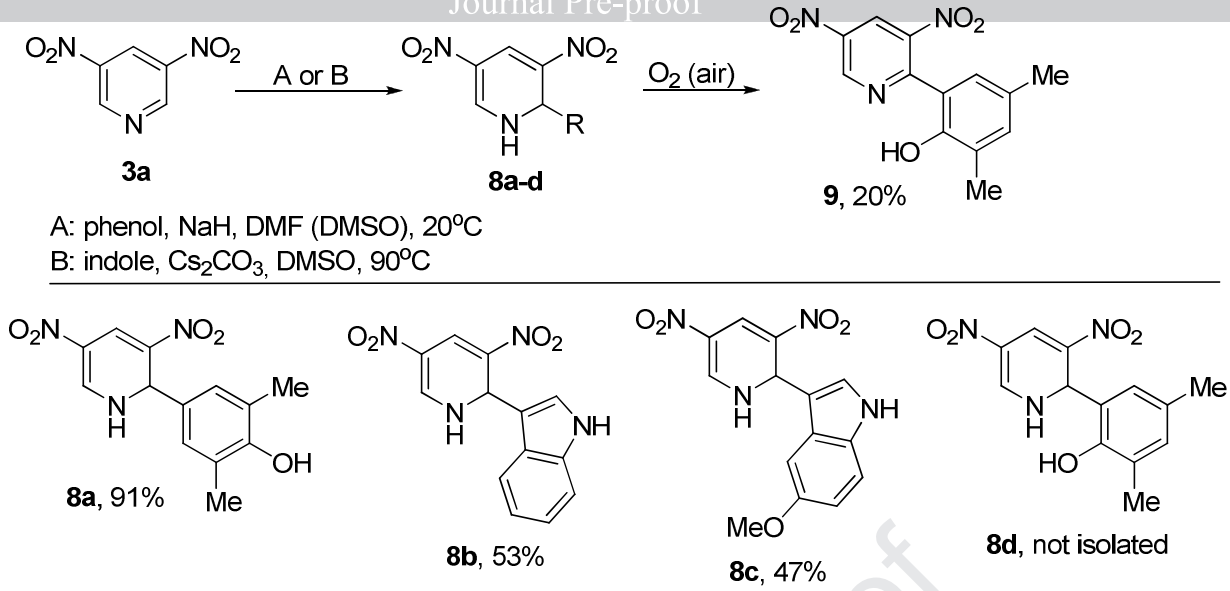


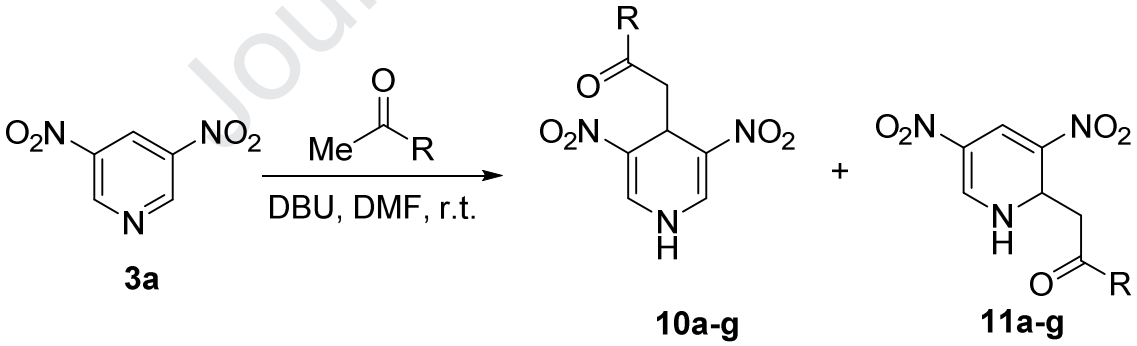
Fig. 1. General view of **6** and solvate water molecule in the crystal. Anisotropic displacement parameters are drawn at the 50% probability level.

Some other π-excessive aromatics such as substituted phenols or indoles react with **3a** similarly giving rise to 2-substituted 1,2-dihydropyridines **8a-d**, scheme 5. However in case of 2,4-dimethylphenol, the addition product **8d** could not be isolated due to its spontaneous oxidative rearomatization to give compound **9**:



Scheme 5. Reaction of 3,5-dinitropyridine **3a** with substituted phenols and indoles.

Another interesting result was obtained using methyl ketones as C-nucleophiles which react smoothly with 3,5-dinitropyridine **3a** in the presence of DBU leading to the mixtures of 1,4- and 1,2-adducts, scheme 6, table 2. 1,4-Dihydropyridines **10a-g** were found to be the major products in all cases, while 1,2-adducts **11** in some cases were formed in trace amounts and could be detected only by NMR of the reaction mixture, table 2. The ratio of isomers **10** and **11** (determined by NMR of crude products) is correlated to some extent with pKa of the corresponding ketone [32]. However, the reasons of such selectivity require additional study.



Scheme 6. Reaction of 3,5-dinitropyridine **3a** with methyl ketones

Table 2. Yields and isomer ratio of compounds **10a-h**, **11a-h**

R	Products	Yield of the mixture (%)	Isomer ratio **10:11***	Isolated yield of major isomer	minor isomer	pKa (DMSO)
Me	**10a+11a**	62	5.9	50	-	26.5
cyclopropyl	**10b+11b**	85	5.0	69	12	-

t-Bu	**10c+11c**	65	4.7	52	-	27.7
Ph	**10d+11d**	88	3.6	67	17	24.7
4-MeO-C_6H_4	**10e+11e**	69	3.6	52	13	25.7
4-Me-C_6H_4	**10f+11f**	83	3.3	62	17	25.2
2-Cl-C_6H_4	**10g+10g**	71	2.1	47	21	23.2

* determined by NMR spectroscopy

The structures of adducts **10** and **11** were established on the basis of NMR spectroscopy, and for compound **10e** it was also confirmed by X-Ray data. (Fig. 2).

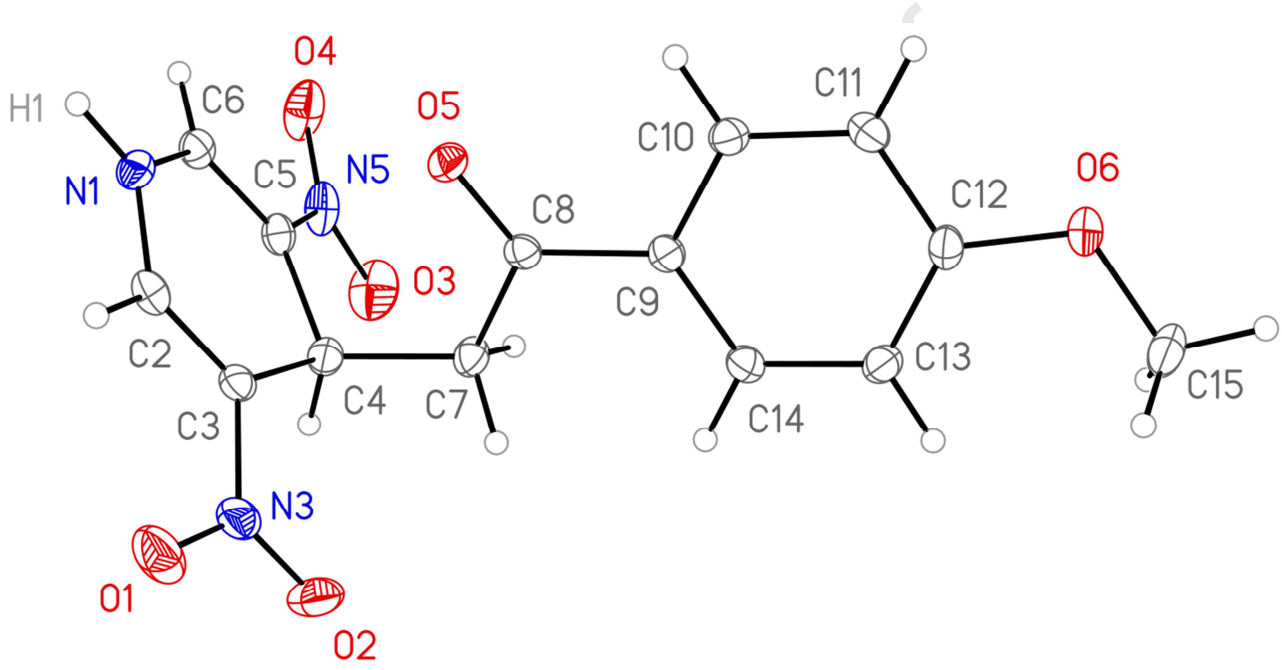
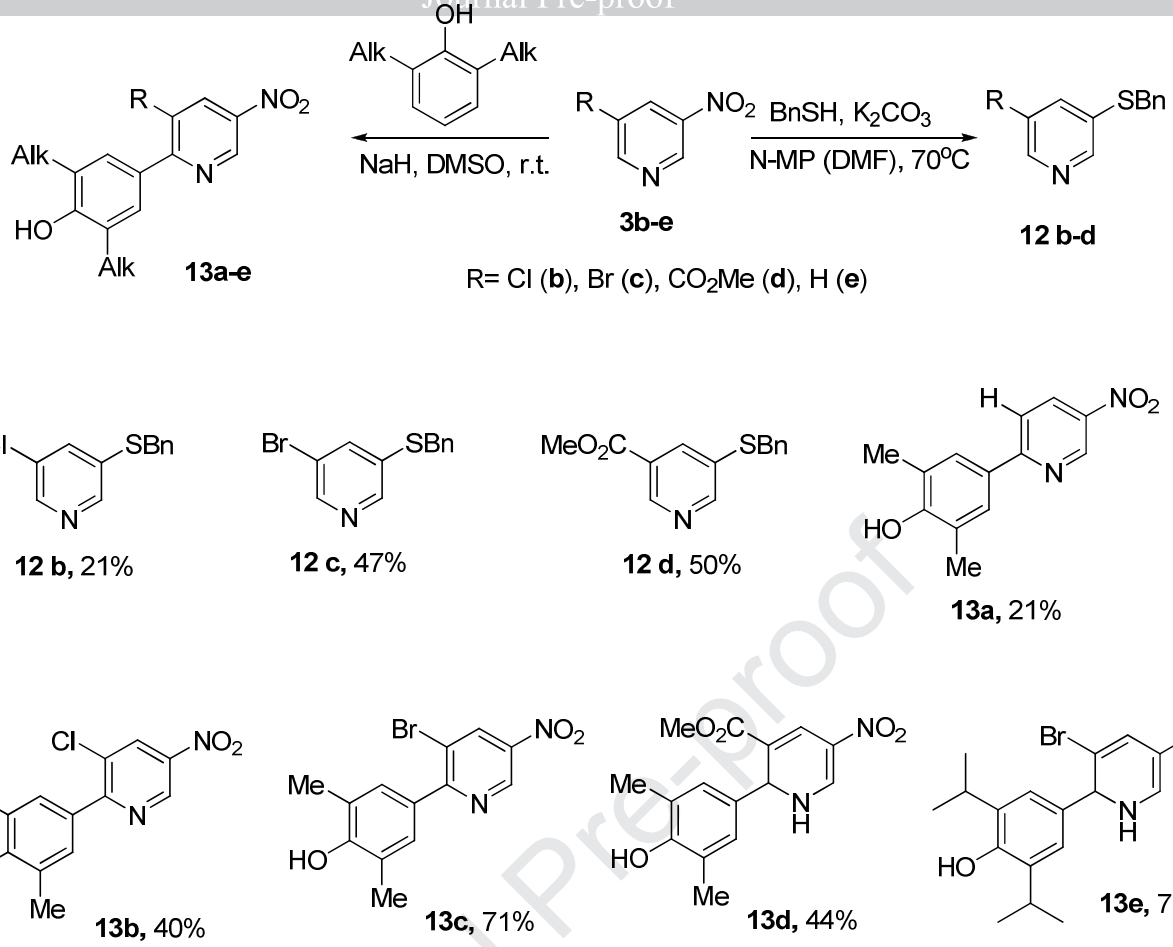


Fig. 2 General view of one of crystallographically independent molecules in the crystal of **10e**. Anisotropic displacement parameters are drawn at the 50% probability level.

The above mentioned functionalization methods of the pyridine ring were extended to 3-R-5-nitropyridines **3b-d**. These compounds were found to undergo nucleophilic substitution of the nitro group with BnSH to form sulfides **12b-d** in moderate yields. In case of compounds **3b,c** the reactions also proceeded selectively and the substitution of halogen was not observed, scheme 7. On the other hand, compounds **3b-d** as well as 3-nitropyridine **3e** reacted with 2,6-disubstituted phenols leading to 2-aryl-5-nitropyridines **13a-e**, scheme 7. Interestingly, in some cases oxidative re-aromatization under the action of air oxygen occurred (compounds **13a-c**), while compounds **13d,e** were proved to be 1,2-dihydropyridines.



Scheme 7. Reactions of 3-R-5-nitropyridines **3b-d** with nucleophiles.

Conclusion

In conclusion, reactions of 3-R-5-nitropyridines with variety of anionic nucleophiles were studied. Direction of the process was found to be dependent on the nature of certain nucleophile. In case of O-, N- and S-nucleophiles the substitution of non-activated nitro group takes place. Such reactivity resembles that of polynitroarenes with *meta*-positioned nitro groups. At the same time ambident nucleophiles (phenoxide ions, indoles, ketone enolates) gave products of nucleophilic 1,2- or 1,4-addition to the pyridine ring. On this basis a number of novel or hardly accessible pyridines and their dihydro derivatives were synthesized. The crystal structure of adducts was studied. Functionalization methods of nitropyridines developed in this work can be applied to the synthesis of wide range of polyfunctionalized pyridines and related compounds.

Experimental section

All chemicals were of commercial grade and used directly without purification. Melting points were measured on a Stuart SMP 20 apparatus. 1H and 13C NMR spectra were recorded on Bruker AC-

200 (at 200 and 50 MHz, respectively), Bruker AM-300 (at 300.13 and 75.13 MHz, respectively), Bruker Avance DRX 500 (at 500 and 125 MHz, respectively) or Bruker Avance II 600 spectrometer (at 600 and 150 MHz, respectively) in DMSO-d6 or $CDCl_3$ with TMS as internal standard. IR spectra were recorded on BrukerAlpha spectrometer, and the samples were prepared as KBr pellets. HRMS spectra were recorded on a Bruker micrOTOF II mass spectrometer using ESI. All reactions were monitored by TLC analysis using ALUGRAM SIL G/UV254 plates, which were visualized by UV light. Compounds **1a-d** were purchased from commercial suppliers. Data collection for all samples was performed on a Bruker APEX DUO diffractometer equipped with CCD detector (graphite-monochromated MoKα radiation with $\lambda = 0.71073$ Å or CuKα radiation with $\lambda = 1.54178$ Å). A semiempirical absorption correction was applied with the SADABS [33] program using the intensity data of the equivalent reflections. The structures were solved with dual-space approach with SHELXT program [34] and refined by the full-matrix least-squares technique against F^2_{hkl} in anisotropic approximation with SHELXL program [35] software package. Hydrogen atoms connected to N and O atoms were found from difference Fourier synthesis and refined isotropically. Other hydrogen atoms were placed in calculated positions and refined in a riding model with $U_{iso}(H_m) = 1.5U_{eq}(C_m)$ for methyl groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for all other hydrogen atoms. Detailed crystallographic information is provided in Table 3. Structures were deposited to Cambridge Structural Database, CCDC 1919417-1919420 and 1938068-1938069 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures.

General procedure for the synthesis of compounds 2a-d. A solution of an appropriate 2-chloropyridine (5 mmol) in methanol (15 mL) was added dropwise to a pre-cooled solution of hydrazine hydrate (2.42 mL, 50 mmol, 10 eq.) in methanol (10 mL).(**2d** was added in small portions as a suspension due to low solubility). The reaction mixture was stirred at room temperature for 1-2 h until the starting compound was completely consumed (TLC). The precipitate was filtered off, washed with water and dried on air.

2-Hydrazino-3,5-dinitropyridine (2a)

Violet solid; yield 75%; m.p. 177^{o}C (lit. 173^{o}C)[36]; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.19 (s, 1H), 8.88 (s, 1H), 7.38 (br.s, 3H).

5-Chloro-2-hydrazino-3-nitropyridine (2b)

Orange solid; yield 78%; m.p. 136-137^{o}C (lit. 134-135^{o}C)[37]; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.46 (br. s, 1H), 8.56 (s, 1H), 8.45 (s, 1H), 4.90 (s, 2H).

5-Bromo-2-hydrazino-3-nitropyridine (2c)

Red solid; yield 89%; m.p. 151 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.39 (br. s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 4.90 (s, 2H).

Methyl 6-hydrazino-5-nitronicotinate (2d)

Red solid; yield 84%; m.p. 167^{o}C (lit. 169-170^{o}C)[37]; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.12 (br.s, 1H), 8.88 (s, 1H), 8.68 (s, 1H), 5.26 (s, 2H), 3.84 (s, 3H).

General procedure for the synthesis of compounds 3a-d. An appropriate 2-hydrazinopyridine (10 mmol) was added to a solution of silver nitrate (5.1 g, 30 mmol) in distilled water (100 mL). The suspension was heated to 80°C with vigorous stirring to prevent excessive foaming. After the evolution of nitrogen ceased, the reaction mixture was heated additionally for 1-2 hours until the starting compound was completely consumed (TLC). A precipitate of metallic silver was filtered off and washed with chloroform. The filtrate was extracted with chloroform, combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated. Traces of colored impurities, if present, can be removed from chloroform solution by shaking with activated charcoal.

3,5-Dinitropyridine (3a)

Pale yellow solid; Yield 70%; m.p. 108-109^{o}C (lit.106^{o}C) [37]; ^{1}H NMR (300 MHz, DMSO): δ= 9.73(s, 2H), 9.13 (s, 1H).

3-Chloro-5-nitropyridine (3b)

White fluffy crystals; yield 62%; m.p. 88-89^{o}C (lit.88) [37]; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.36 (s, 1H), 8.91 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO): δ= 154.2, 145.0, 143.4, 131.9, 131.8.

3-Bromo-5-nitropyridine (3c)

Off-white solid; yield 84%; m.p. 113-114 °C (lit. 110°C) [38]; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.38 (s, 1H), 9.00 (s, 1H), 8.65 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 156.8, 145.1, 143.8, 134.4, 121.3. HRMS (ESI): *m/z* calcd for $C_5H_3BrN_2O_2$ [M+H]: 202.9451 ; found: 202.9448.

Methyl 5-nitronicotinate (3d)

Yellow solid; Yield 51%; m.p. 88 °C (lit 87°C) [39]; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.60 (s, 1H), 9.50 (s, 1H), 9.05 (s, 1H), 4.05 (s, 3H).

General procedure for the synthesis of compounds 4a-c, 12b-d. To a solution of appropriate 3-nitropyridine (1 mmol) in DMF or NMP (5 mL) was added an appropriate thiol (1.5 mmol), K_2CO_3 (0.138 g, 1 mmol) and the reaction mixture was stirred at 70°C until the starting compound was completely consumed (TLC), then poured into water, acidified to pH 2~3 with concentrated hydrochloric acid and extracted with chloroform. Organic phase was washed several times with water, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash-chromatography on silica gel with chloroform as eluent.

3-(Benzylthio)-5-nitropyridine (4a)

Beige solid; yield 34%; m.p. 72-73 °C; ^{1}H NMR (200 MHz, DMSO-d6): δ= 9.12 (s, 1H) 8.87 (s, 1H), 8.48 (s, 1H), 7.42-7.25 (m, 5H), 4.47 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 153.5, 142.3, 136.3, 135.3, 129.9, 129.3, 128.9, 128.6, 127.4, 35.9. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}N_2O_2S$ [M+H]: 247.0536; found: 247.0532.

3-[(2-Furylmethyl)thio]-5-nitropyridine (4b)

Brown crystals; yield 36%; m.p. 70-71 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.17 (s, 1H), 8.91 (s, 1H), 8.55 (s, 1H), 7.61 (s, 1H), 6.38 (s, 1H), 6.33 (s, 2H), 4.55 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 154.0, 149.6, 144.2, 143.1, 141.6, 134.5, 130.5, 110.7, 108.9, 28.7. (ESI): *m/z* calcd for $C_{10}H_8N_2O_3S$ [M+H]: 237.0328; found: 237.0328.

3-(Cyclohexylthio)-5-nitropyridine (4c)

Beige solid; yield 59%; m.p. 72 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.18 (s, 1H), 8.93 (s, 1H), 8.49 (s, 1H), 3.55-3.63 (m, 1H), 1.97 (s, 2H), 1.72 (s, 2H), 1.60 (d, *J* = 11.7 Hz, 1H), 1.47-1.25 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d6): δ 155.0, 144.3, 141.7, 134.1, 131.4, 44.6, 32.4, 25.1. HRMS (ESI): *m/z* calcd for $C_{11}H_{14}N_2O_2S$ [M+H]: 239.0849; found: 239.0844.

3-(Isobutylthio)-5-nitropyridine (4d)

Brown solid; yield 48%; m.p. 60 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.13 (d, *J* = 2.1 Hz, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.45 (s, 1H), 3.10 (d, *J* = 6.6 Hz, 2H), 1.92-1.83 (m, 1H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 154.2, 145.6, 141.9, 137.6, 130.2, 41.1, 28.8, 22.8. HRMS (ESI): *m/z* calcd for $C_8H_{10}N_2O_2S$ [M+H]: 213.0692; found: 213.0692.

3-(Benzylthio)-5-chloropyridine (12b)

Red oil; yield 21%; ^{1}H NMR (300 MHz, DMSO-d6): δ= 8.43 (s, 1H), 8.40 (d, *J* = 1.5 Hz, 1H), 7.93 (s, 1H), 7.37-7.22 (m, 5H), 4.36 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 147.0, 145.1, 136.6, 135.0, 128.8, 128.4, 127.3, 36.0. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}ClNS$ [M+H]: 236.0295; found: 236.0303.

3-(Benzylthio)-5-bromopyridine (12c)

Red oil; yield 47%; ^{1}H NMR (300 MHz, DMSO-d6): δ= 8.48 (s, 1H), 8.46 (s, 1H), 8.04 (s, 1H), 7.41-7.22 (m, 5H), 4.36 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 147.8, 138.3, 137.1, 135.9, 129.4, 129.1, 129.0, 127.8, 120.7, 36.6. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}BrNS$ [M+H]: 279.9790; found: 279.9792.

Methyl 5-(benzylthio)nicotinate (12d)

Light-brown solid; yield 50%; m.p. 69-70^{o}C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 8.84 (s, 1H), 8.71 (s, 1H), 8.14 (s, 1H), 7.36-7.23 (m, 5H), 4.37 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 165.2, 153.3, 147.5, 137.2, 136.7, 134.2, 129.4, 129.0, 127.8, 126.1, 53.0, 36.9. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}NO_2S$ [M+H]: 260.0740; found: 260.0740.

3-Methoxy-5-nitropyridine (4e)

To a solution of 3,5-dinitropyridine (0.169 g, 1 mmol) in MeOH (10 mL) was added powdered MeONa (0.162 g, 3 mmol) and the reaction mixture was refluxed until the starting compound was completely consumed (TLC), then poured into water and extracted with ethyl acetate. Organic phase was washed several times with water, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash-chromatography on silica gel with chloroform as eluent.

Light-brown solid; yield 30%; m.p. 72-73 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 8.99 (s, 1H), 8.72 (s, 1H), 8.11 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 155.6, 144.8, 144.1, 136.2, 114.7, 56.5. HRMS (ESI): *m/z* calcd for $C_6H_6N_2O_3$ [M+H]: 155.0451; found: 155.0455.

3-Azido-5-nitropyridine (4f)

To a solution of 3,5-dinitropyridine (0.169 g, 1 mmol) in DMF (5 mL) was added NaN_3 (0.195 g, 3 mmol) and the reaction mixture was stirred at 85°C until the starting compound was completely consumed (TLC), then poured into water and extracted with ethyl acetate. Organic phase was washed several times with water, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash-chromatography on silica gel with chloroform as eluent.

Light-yellow solid; yield 48%; m.p. 36^{o}C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.16 (d, *J* = 2.1 Hz, 1H), 8.81 (d, *J* = 2.2 Hz, 1H), 8.34 (t, *J* = 2.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d6): δ= 146.7, 144.5, 140.3, 138.0, 121.8. IR (KBr, νmax/cm-1): 682, 814, 900, 1175, 1288, 1317, 1357, 1530, 1568, 2138. HRMS (ESI): *m/z* calcd for $C_5H_3N_5O_2$ [M+H]: 166.0360; found: 166.0366.

1-Phenylethan-1-one O-(5-nitropyridin-3-yl) oxime (4g)

3,5-dinitropyridine (0.169 g, 1 mmol) and acetophenone oxime (0.135 g, 1 mmol) were dissolved in DMSO (10 mL) and NaH (60% in mineral oil, 0.04 g, 1 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours until the starting compound was completely consumed (TLC), then poured into water and acidified to pH 2~3 with hydrochloric acid. A precipitate was filtered off, washed with water and dried on air.

Yellow solid; yield 67%; m.p. 90°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.11 (s, 1H), 9.00 (s, 1H), 8.41 (s, 1H), 7.87 (d, *J* = 6.5 Hz, 2H), 7.54 (m, 3H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 161.6, 155.2, 144.7, 142.8, 138.0, 134.3, 130.7, 128.8, 126.8, 116.3, 13.7. HRMS (ESI): *m/z* calcd for $C_{13}H_{11}N_3O_3$ [M+H]: 258.0873; found: 258.0861.

General procedure for the synthesis of compounds 6,8a,9,14a-e To a solution of sodium phenoxide prepared from substituted phenol (1 mmol) and NaH (60% in mineral oil, 0.04 g, 1 mmol) in DMSO (10 mL), was added an appropriate 3-nitropyridine (1 mmol). The reaction mixture was stirred at room temperature for 1-24 hours until the starting compound was completely consumed (TLC), then poured into water and acidified to pH 2~3 with hydrochloric acid. A precipitate was filtered off, washed with water and dried in air.

4-(3,5-Dinitro-1,2-dihydropyridin-2-yl)phenol (6)

Red crystals; yield 15%; m.p. 222°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.82 (br.s, 1H), 9.67 (s, 1H), 8.64 (s, 1H), 8.32 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.04 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 158.1, 147.8, 130.7, 130.1, 128.6, 125.3, 118.9, 115.6, 55.1; HRMS (ESI): *m/z* calcd for $C_{11}H_9N_3O_5$ [M+Na]: 286.0434 ; found: 286.0441.

4-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-2,6-dimethylphenol (8a)

Orange powder; yield 91%; m.p. 264°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.79 (br.s., 1H), 8.60 (s, 1H), 8.49 (s, 1H), 8.32 (s, 1H), 6.97 (s, 2H), 5.97 (s, 1H), 2.16 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 154.0, 147.7, 130.6, 130.2, 127.1, 125.4, 124.7, 118.9, 55.4, 16.5; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_3O_5$ [M+H]: 292.0928 ; found: 292.0929.

2-(3,5-Dinitropyridin-2-yl)-4,6-dimethylphenol (9)

Red crystals; yield 20%; m.p. 172°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.38 (s, 1H), 8.90 (s, 1H), 7.81 (s, 1H), 7.41 (s, 1H), 2.53 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 158.0, 149.7, 148.8, 143.4, 142.1, 135.5, 135.0, 123.3, 122.0, 119.9, 116.1, 21.9, 15.6; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}N_3O_5$ [M+H]: 290.0771 ; found: 290.0770.

2,6-Dimethyl-4-(5-nitropyridin-2-yl)phenol (13a)

Brown solid; yield 21%; m.p. 186-187°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.33 (s, 1H), 8.94 (s, 1H), 8.53 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 2H), 2.56 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 161.4, 156.5, 144.8, 142.0, 132.3, 128.1, 127.3, 124.8, 119.1, 16.8; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}N_2O_3$ [M+H]: 245.0921 ; found: 245.0921.

4-(3-Chloro-5-nitropyridin-2-yl)-2,6-dimethylphenol (13b)

Yellow solid; yield 40%; m.p. 145-147°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.32 (s, 1H), 8.89 (s, 1H), 8.75 (s, 1H), 7.44 (s, 2H), 2.24 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 160.5, 155.5, 142.5, 142.2, 133.5, 129.9, 128.4, 127.0, 123.9, 16.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}ClN_2O_3$ [M+H]: 279.0531 ; found: 279.0530.

4-(3-Bromo-5-nitropyridin-2-yl)-2,6-dimethylphenol (13c)

^{1}H NMR spectrum contains trace signals (5%) of **4a** as a minor product. Yellow solid; yield 71%; m.p. 140-143°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.33 (s, 1H), 8.85 (s, 1H), 8.83 (s, 1H), 7.38 (s, 2H), 2.23 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 162.2, 155.2, 142.9, 142.1, 136.5, 129.9, 128.4, 123.8, 117.8, 16.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}BrN_2O_3$ [M+H]: 323.0026 ; found: 323.0026.

Methyl 2-(4-hydroxy-3,5-dimethylphenyl)-5-nitro-1,2-dihydropyridine-3-carboxylate (13d)

Light-red crystals; yield 44%; m.p. 235°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.99 (bs, 1H), 8.41 (s, 1H), 8.40 (bs, 1H), 7.81 (s, 1H), 6.85 (s, 2H), 5.49 (s, 1H), 3.61 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 164.9, 153.5, 146.6, 132.3, 127.1, 126.8, 124.4, 120.0, 112.5, 54.9, 51.6, 16.6; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}N_2O_5$ [M+H]: 305.1132 ; found: 305.1132.

4-(3-Bromo-5-nitro-1,2-dihydropyridin-2-yl)-2,6-diisopropylphenol (13e)

Yellow solid; yield 75%; m.p. 166°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 9.53 (br. s. 1H), 8.26 (s, 1H), 7.15 (s, 1H), 6.98 (s, 2H), 5.46 (s, 1H), 3.24-3.29 (m, 2H), 1.12 (d, *J*= 6.6 Hz, 12H); ^{13}C NMR (75.47 MHz, DMSO-d6): δ 151.8, 143.6, 136.0, 131.8, 122.8, 121.0, 119.9, 109.5, 62.8, 26.7, 23.4, 23.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}BrN_2O_3$ [M+H]: 381.0808 ; found: 381.0799.

General procedure for the synthesis of compounds 8b-c. An appropriate indole (1 mmol) was added to a solution of 3,5-dinitropyridine (0.169 g, 1 mmol) in DMF (5 mL), followed by Cs_2CO_3 (0.326 g, 1 mmol). The reaction mixture was stirred at 70°C for 2-3 hours until the starting compound was completely consumed (TLC), then poured into diluted hydrochloric acid and extracted several times with ethyl acetate. Combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from ethanol.

3-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-1H-indole (8b)

Red powder; yield 47%.; m.p. 236-237°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 11.30 (s, 1H), 10.85 (bs, 1H), 8.61 (s, 1H), 8.31 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.16-7.04 (m, 2H), 6.47 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 147.5, 136.4, 130.1, 125.5, 125.4, 124.7, 121.7, 119.6, 119.1, 118.5, 113.8, 112.1, 48.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_4O_4$ [M+H]: 287.0775; found: 287.0779.

3-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-5-methoxy-1H-indole (8c)

Red powder; yield 53%; m.p. 208°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 11.19 (s, 1H), 10.86 (bs,1H), 8.65 (s, 1H), 8.34 (s, 1H), 7.41 (s, 1H), 7.32 (d, *J* = 9 Hz, 1H), 7.09 (s, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.45 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): δ= 153.6, 147.4, 131.5, 129.7, 125.8, 125.0, 124.6, 119.2, 113.5, 112.7, 111.6, 100.9, 55.1, 48.5; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_4O_5$ [M+H]: 317.0880 ; found: 317.0881.

General procedure for the synthesis of compounds 10a-g, 11a-g. An appropriate methylketone (1 mmol) was added to a solution of 3,5-dinitropyridine (0.169 g, 1 mmol) in DMF (5 mL) followed by DBU (0.300 mL, 2 mmol). The reaction mixture was stirred at room temperature for 1-3 hours until the starting compound was completely consumed (TLC), then poured into diluted hydrochloric acid. An oily precipitate was dissolved in ethyl acetate and water phase was additionally extracted several times with ethyl acetate. Combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash-chromatography on silica gel with ethyl acetate/chloroform 1:1 as eluent.

1-(3,5-Dinitro-1,4-dihydropyridin-4-yl)propan-2-one (10a)

Brownish-yellow solid; yield 50%; m.p. 176-178°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.39 (bs, 1H), 8.04 (s, 2H), 4.77 (t, *J* = 4.2 Hz, 1H), 2.75 (d, *J* = 4.2 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6): δ= 205.6, 135.5, 130.5, 45.4, 30.9, 29.9; HRMS (ESI): *m/z* calcd for $C_8H_9N_3O_5$ [M+K]: 266.0174; found: 266.0178.

1-(3,5-Dinitro-1,2-dihydropyridin-2-yl)propan-2-one (11a)

Not isolated in pure form; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.39 (bs, 1H), 8.40 (s, 1H), 8.11 (s, 1H), 5.43 (dd, J_1 = 8.9 Hz, J_2 = 2.2 Hz, 1H), 3.15 (dd, J_1 = 17.7 Hz, J_2 = 9 Hz, 1H), 2.81 (d, *J* = 11.6 Hz, 1H), 2.12 (s, 3H).

1-Cyclopropyl-2-(3,5-dinitro-1,4-dihydropyridin-4-yl)ethan-1-one (10b)

Yellow crystals; yield 69%; m.p. 145-146 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.38 (bs, 1H), 8.03 (s, 2H), 4.83 (t, *J* = 4.2 Hz, 1H), 2.85 (d, *J* = 4.2 Hz, 2H), 1.98-1.90 (m, 1H), 0.87-0.73 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 207.8, 135.6, 130.3, 44.3, 31.4, 20.7, 10.7.= HRMS (ESI): *m/z* calcd for $C_{10}H_{11}N_3O_5$ [M+K]: 292.0330; found: 292.0336.

1-Cyclopropyl-2-(3,5-dinitro-1,2-dihydropyridin-2-yl)ethan-1-one (11b)

Red oil; yield 12%; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.36 (bs, 1H), 8.41 (s, 1H), 8.11 (s, 1H), 5.46 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 3.25 (dd, J_1 = 17.9 Hz, J_2 = 8.7 Hz, 1H), 2.89 (dd, J_1 = 17.7 Hz, J_2 = 2.6 Hz, 1H), 2.01 (m, 1H), 0.91-0.83 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d6): δ 207.3, 149.7, 128.8, 126.3, 120.0, 48.4, 46.5, 20.8, 10.8, 10.7.

1-(3,5-Dinitro-1,4-dihydropyridin-4-yl)-3,3-dimethylbutan-2-one (10c)

Brown powder; yield 52%; m.p. 190°C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.39 (bs, 1H), 8.03 (s, 2H), 4.80 (t, *J* = 3.9 Hz ,1H), 2.87 (d, *J* = 3.9 Hz, 2H), 0.97 (s, 12H); ^{13}C NMR (150 MHz,

DMSO-d6): δ= 213.6, 136.8, 131.7, 45.4, 38.7, 32.3, 26.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{15}N_3O_5$ [M+K]: 308.0643; found: 308.0643.

1-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-3,3-dimethylbutan-2-one (11c)

Not isolated in pure form; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.39 (bs, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 5.44 (d, J = 8.6 Hz, 1H), 3.11 (s, 1H), 2.83 (s, 1H), 1.06 (s, 12H).

2-(3,5-Dinitro-1,4-dihydropyridin-4-yl)-1-phenylethan-1-one (10d)

Orange crystals; yield 67%; m.p. 187-188 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.42 (bs, 1H), 8.04 (s, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.2 Hz , 1H), 7.51 (t, *J* = 7.5 Hz ,2H), 4.99 (t, *J* = 4.5 Hz ,1H), 3.29 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d6): δ= 197.4, 136.6, 135.6, 133.3, 130.2, 128.8, 127.9, 40.7, 31.9; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}N_3O_5$ [M+H]: 290.0771 ; found: 290.0772.

2-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-1-phenylethan-1-one (11d)

Red oil; yield 17%; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.45 (bs, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 7.99 (d, *J* = 8 Hz, 2H), 7.67 (m, 1H), 7.54 (m, 2H), 5.67 (d, *J* = 7.8 Hz, 1H), 3.80 (dd, J_1 = 17.8 Hz, J_2 = 8.7 Hz, 1H), 3.32 (s, 1H).

2-(3,5-Dinitro-1,4-dihydropyridin-4-yl)-1-(4-methoxyphenyl)ethan-1-one (10e)

Orange crystals; yield 52%; m.p. 174 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.38 (bs, 1H), 8.02 (s, 2H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz), 4.96 (t, *J* = 4.8 Hz, 1H), 3.83 (s, 3H), 3.21 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d6): δ= 195.8, 163.3, 135.6, 130.3, 130.2, 129.7, 114.0, 55.6, 40.0, 32.1; HRMS (ESI): *m/z* calcd for $C_{14}H_{13}N_3O_6$ [M+H]: 320.0877 ; found: 320.0869.

2-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-1-(4-methoxyphenyl)ethan-1-one (11e)

Red oil; yield 13%; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.38 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.91 (s, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.77 (s, 1H), 3.89 (s, 3H), 3.53 (d, *J* = 2 Hz, 1H), 3.50 (s, 1H).

2-(3,5-Dinitro-1,4-dihydropyridin-4-yl)-1-(p-tolyl)ethan-1-one (10f)

Orange crystals; yield 62%; m.p. 153-154 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.40 (bs, 1H), 8.02 (s, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 4.96 (t, *J* = 4.5 Hz, 1H), 3.24 (d, *J* = 4.8 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6): δ= 196.9, 143.7, 135.6, 134.2, 130.2, 129.3, 128.1, 40.4, 32.0, 21.2; HRMS (ESI): *m/z* calcd for $C_{14}H_{13}N_3O_5$ [M+H]: 304.0928 ; found: 304.0928.

2-(3,5-Dinitro-1,2-dihydropyridin-2-yl)-1-(p-tolyl)ethan-1-one (11f)

Red oil; yield 17%; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.36 (s, 1H), 8.31 (d, *J* = 7.3 Hz, 1H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.75 (s, 1H), 7.25 (d, *J* = 6.5 Hz, 2H), 5.74 (s, 1H), 3.52 (d, *J* = 5.2 Hz, 2H), 2.40 (s, 3H).

1-(2-Chlorophenyl)-2-(3,5-dinitro-1,4-dihydropyridin-4-yl)ethan-1-one (10g)

Orange crystals; yield 47%; m.p. 164-165 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.43 (bs, 1H), 8.03 (s, 2H), 7.57-7.38 (m, 4H), 4.94 (t, *J* = 3.9 Hz, 1H), 3.32 (d, *J* = 3.9 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d6): δ= 201.0, 139.4, 136.9, 133.6, 131.6, 131.3, 130.8, 130.6, 128.5, 44.9, 32.7; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}ClN_3O_5$ [M+NH_4]: 341.0647 ; found: 341.0647.

1-(2-Chlorophenyl)-2-(3,5-dinitro-1,2-dihydropyridin-2-yl)ethan-1-one (11g)

Red oil; yield 21%; ^{1}H NMR (300 MHz, DMSO-d6): δ= 10.52 (bs, 1H), 8.47 (s, 1H), 8.12 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.56 (s, 1H), 7.55 (s, 1H), 7.46 (m, 1H), 5.65 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 3.71 (dd, J_1 = 17.9 Hz, J_2 = 8.2 Hz, 1H), 3.28 (dd, J_1 = 17.9 Hz, J_2 = 2.7 Hz, 1H).

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- ✓ Reactions of 3-R-5-nitropyridines with nucleophiles were investigated
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- ✓ Interaction with ambident nucleophiles leads to dearomatization of pyridine ring
- ✓ A number of novel or hardly accessible pyridine derivatives were synthesized
- ✓ Methods for the synthesis of polyfunctionalized pyridines were developed