

# Synthetic pathways to a family of pyridine-containing azoles - promising ligands for coordination chemistry

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**Dedicated to Professor N. S. Zefirov on the occasion of his 70<sup>th</sup> birthday**

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## Abstract

A series of pyridine-containing pyrazoles, isoxazoles, imidazoles, oxazoles, thiazoles, oxadiazoles, triazoles, and 1,3,4-triazepines were synthesized and characterized with the aim of their future study as conjugated building blocks for the construction of coordination compounds.

**Keywords:** Pyridine, azoles, coordination polymers

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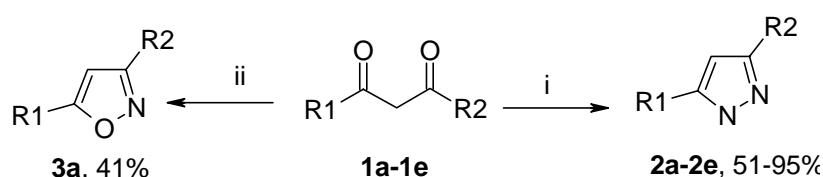
## Introduction

The design of coordination polymeric frameworks with unique structures and valuable application properties is a topical area in comprehensive coordination and material chemistry.<sup>1,2</sup> Many studies are concentrated on metal complexes based on pyridyl-bearing ligands. These ligands are represented by the general formula Py–X–Py, where X is a conjugating unit between two exo-dentate pyridines. The simplest ligand of this type is 4,4'-bipyridyl, which is widely used in constructing coordination polymers.<sup>3</sup> Typical X's are C=C and C≡C bonds, azo- and imine-groups, benzene, triazine and tetrazine rings, or a combination of the fragments listed.<sup>4</sup> Recently, several research groups published papers on the coordination ability of polydentate ligands based on five-membered azoles as a central linker between two pyridines.<sup>5,6,7,8</sup>

In this paper we describe our study on the synthesis and characterization of several groups of expanded bipyridines (Py–X–Py type molecules) based on a five-membered heterocyclic central fragment X. We focused our efforts on pyridine-containing pyrazoles, isoxazoles, imidazoles, oxazoles, thiazoles, oxadiazoles, triazoles, and 1,3,4-triazepines.

## Results and Discussion

General synthetic routes to 1,2-azoles include the reaction of bis-nucleophiles with  $\beta$ -diketones. Pyridine-containing pyrazoles and isoxazoles are the most investigated class among pyridine-containing azoles, which is due to the synthetic availability of various  $\beta$ -diketones. Using the known procedures for the synthesis of dipyrindinepyrazoles **2a-2c**,<sup>9</sup> new aryl and donor-type hetaryl substituted pyrazoles **2d**, **2e** were synthesized (Scheme 1). The yields of the reactions are in good accordance with the electronic influence of the pyridine moiety, except for product **2c** where the stability of the diketone is crucial for the yield. The approach shown is also valuable for the preparation of *sym*-isoxazole **3a**, which could be easily isolated in moderate yield after heating of the appropriate  $\beta$ -diketone with hydroxylamine (see Scheme 1).



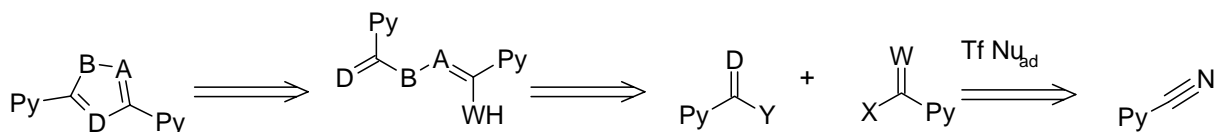
i-  $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ , EtOH, reflux; ii –  $\text{NH}_2\text{OH}$ ,  $\text{K}_2\text{CO}_3$ , EtOH, 80 °C

### Scheme 1

The presence of hydrogen bond donors (N-H groups in a pyrazole ring) and hydrogen bond acceptors (pyridine nitrogens) might result in intermolecular contact within the crystal structures of the products. Indeed, X-ray structural study of **2c**,<sup>10</sup> revealed the existence of hydrogen-bonded dimers, which stack along the crystallographic axis, whereas for the compound **2a** infinite head-to-tail chains were found.<sup>11</sup>

Azachalcones look like the obvious precursors for the synthesis of *unsym*-isoxazole. Recently, we found that the synthesis of azachalcones, starting from acetylpyridines and pyridinecarbaldehydes, is more complicated than it was thought before.<sup>12</sup> For this reason in the present work, *unsym*-isoxazoles were not studied.

For the access to 1,3-diazole and triazole subsystems, one can start from cheap and available cyanopyridine using nucleophilic addition reactions. The cyanopyridine could be easily acylated or alkylated by appropriate pyridine derivatives and the intermediates obtained could then be introduced into the next steps of the heterocycle synthesis (Scheme 2).



A-B = N-NH, N-O, CH-N, CH-S;

D = NH/N\*, NAr, O;

W = NH, O;

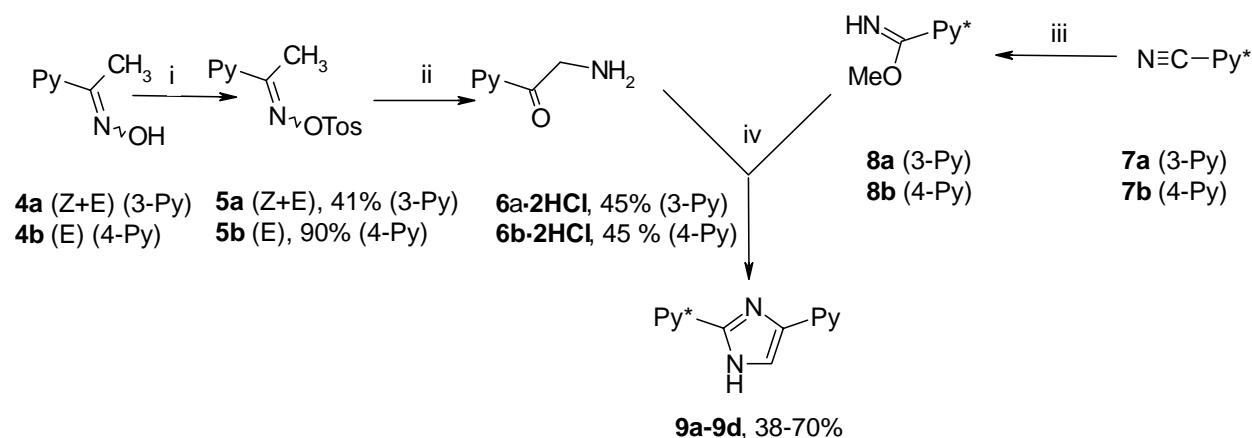
X = NHHN<sub>2</sub>, NH<sub>2</sub>OH, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>Br;

Y = Hal, OMe, SH.

\*depends on "B" nature

## Scheme 2

In the synthesis of the isomers of dipyridylimidazole, the key-substance is 2-pyridyl-2-aminoethanone **6** – the ambiphilic precursor for cyclocondensation (Scheme 3). In spite of the published results,<sup>13,14,15,16</sup> there were some uncertainties about the influence of the electronic and spatial factors of the substrate on the course of the reaction. We found that the yield of the tosylation step (preparation of compounds **5** – see Scheme 3) is more influenced by the configuration of the oxime than by the electronic factors. The next step – the Neber rearrangement – was found to be dependent neither on the electronic nature of the hetaryl substituent nor on the spatial factor. The isolation of the diketal derivative of the aminoketone might result in an increasing yield.<sup>14</sup> The key-step of the reaction, shown in Scheme 3, is based on the reaction of methyl carbimidate **8**, generated *in situ* from the appropriate nitrile **7** and aminoketone **6b**.<sup>17</sup> The target imidazoles **9a-9d** were isolated in moderate to good yields. The main drawback of this method is the formation of the diarylpyrazine, which is the product of autocondensation of **6**.<sup>13</sup>

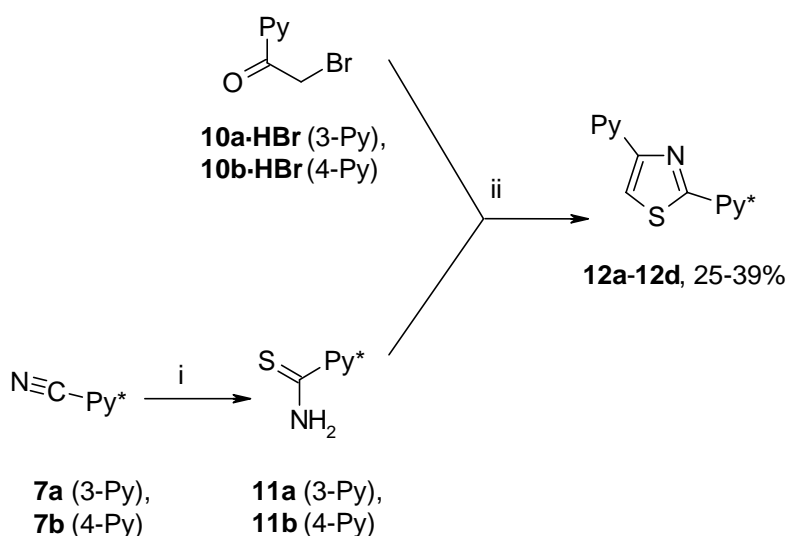


i - TsCl, pyridine, 0 °C; ii – KOEt, rt, 1h, HCl; iii - MeONa, MeOH, rt; iv – AcOH, reflux, 2h

## Scheme 3

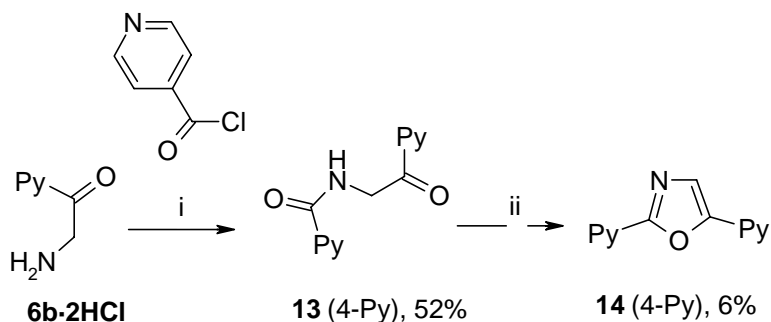
In order to obtain thiazolylpyridines (Scheme 4), we used the S-alkylation of thioamide **11** by easy-available<sup>18</sup>  $\omega$ -bromoketone **10**. Thioamide is also obtained using a literature procedure, which includes catalytic hydrogen sulfide addition to nitrile **7**.<sup>19</sup> We improved the known technique<sup>20</sup> in such a way, that the initially formed insoluble thiouronium salt is separated, and then converted into the thiazole by quenching with triethylamine. In spite of low and moderate yields of **12**, the total outcome for the thiazolylpyridine derivatives was significantly raised as compared to the work cited above.

Our synthetic approach to the oxazole analogue of **12** was based on the preparation of the acyclic intermediate **13**. Unfortunately, the latter was unable to form the 5-membered ring under several different dehydrating conditions (Scheme 5). Finally, the oxazole **14** was the minor product along with the starting material.



i -  $\text{Na}_2\text{S}$ ,  $\text{H}_2\text{S}$ , benzene- $\text{H}_2\text{O}$ ,  $(\text{Cet})\text{Me}_3\text{N}^+\text{Br}$ ; ii -  $\text{Et}_3\text{N}$ ,  $\text{EtOH}$ , reflux.

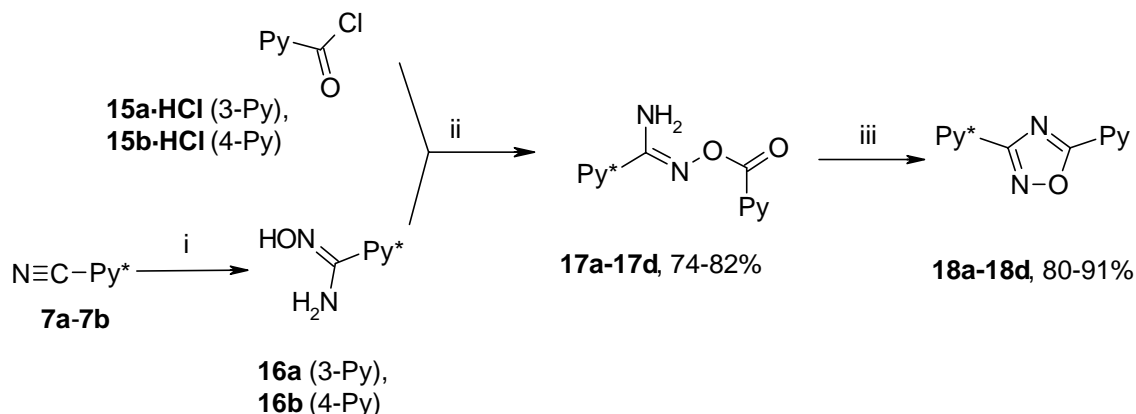
#### Scheme 4



i -  $\text{DMF}$ , heat; ii -  $170^\circ\text{C}$ .

#### Scheme 5

Concerning the azole systems with three heteroatoms, particular attention was paid to the compounds with an oxadiazole ring. In the case of the 1,2,4-oxadiazole subsystem, no significant complications were found. We were lucky to obtain the target 3,5-dipyridyl-derivatives **18** in two steps with high yields (Scheme 6). Starting from commercially available pyridoyl chlorides **15** and available amidoximes **16**, O-pyridoylamidoximes **17** were synthesized.<sup>21,22</sup> These intermediates were then converted into oxadiazole by removal of water by heating.

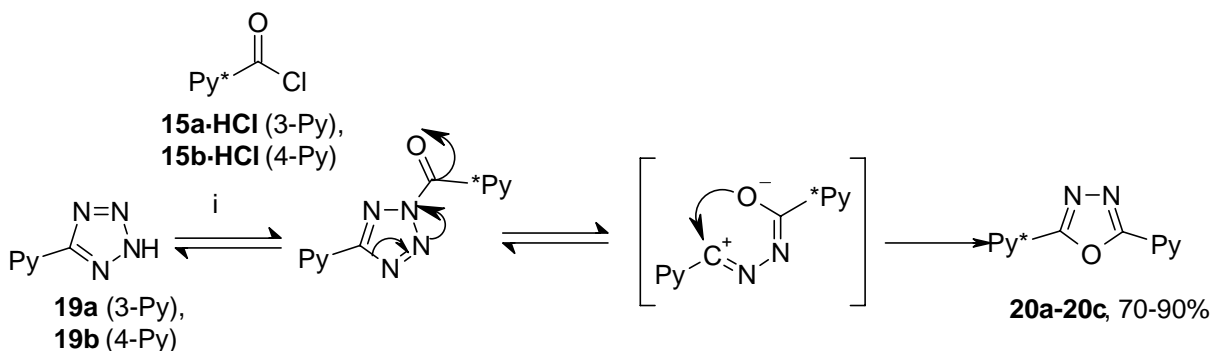


i – NH<sub>2</sub>OH, EtOH, reflux; ii – K<sub>2</sub>CO<sub>3</sub>, acetone; iii – toluene, reflux.

### Scheme 6

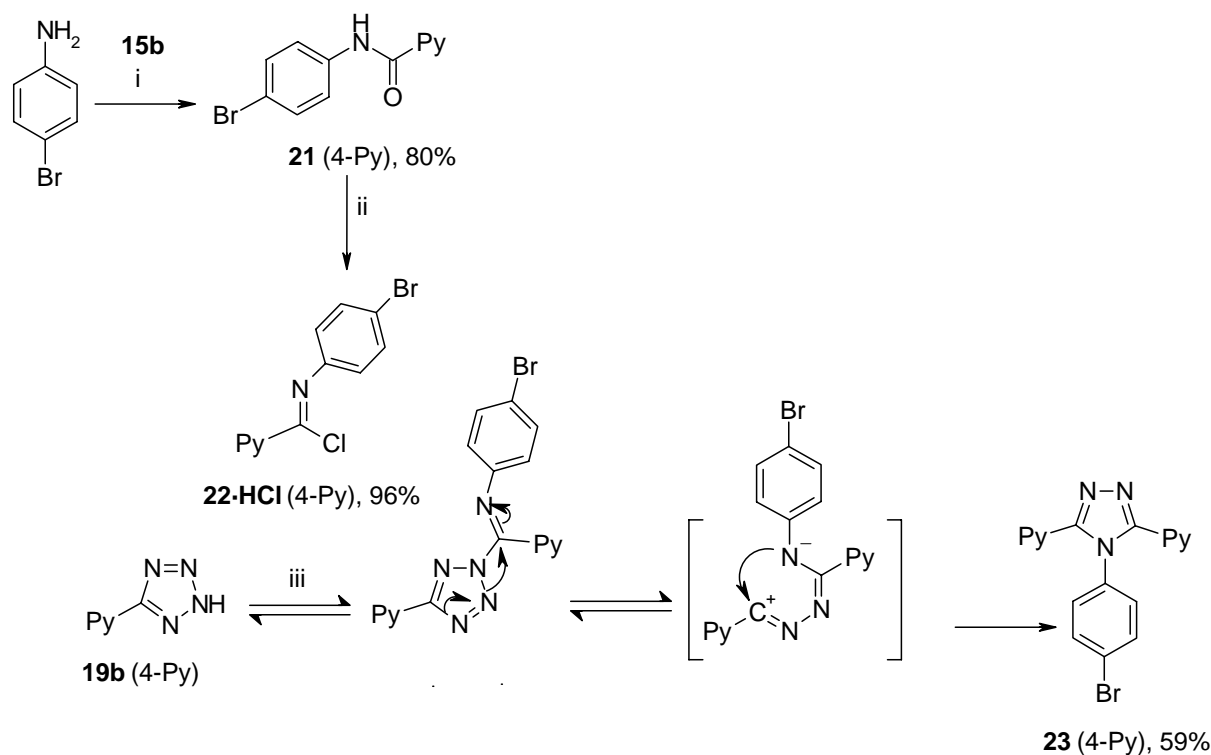
Although pyridine-containing 1,3,4-oxadiazoles were already mentioned in the literature,<sup>23,24</sup> we adopted a novel method<sup>25</sup> for their preparation *via* a dipolar intermediate (Scheme 7). In this case 5-pyridyl-tetrazole **19** could be regarded as the nucleophilic adduct of the azide-anion and the appropriate nitrile. The nature of the substituent at C<sup>5</sup> influenced the product yield to a negligible extent. We also conducted this reaction under microwave irradiation and found that yields were higher and shorter reaction times were required.

The 4-aryl substituted triazole **23** was obtained in the same manner in three steps, starting from 4-bromoaniline and tetrazole **19b** (Scheme 8). In this case, the reaction mixture was contaminated with several side-products that were not identified.



i - pyridine, 70 °C, 20 min/ pyridine, MW<sub>irr</sub>, -30 s.

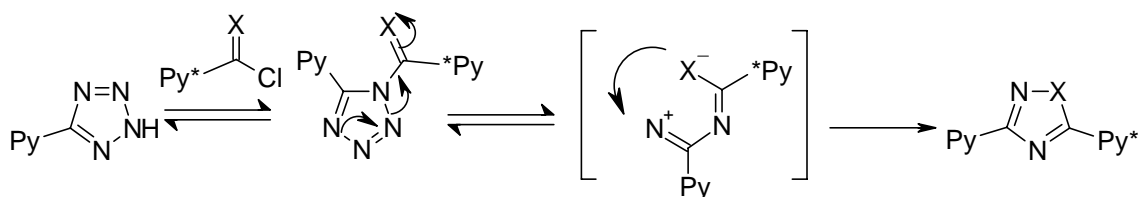
### Scheme 7



i – DMF, heat; ii –  $\text{PCl}_5$  reflux; iii - pyridine, 60 °C, 20 min

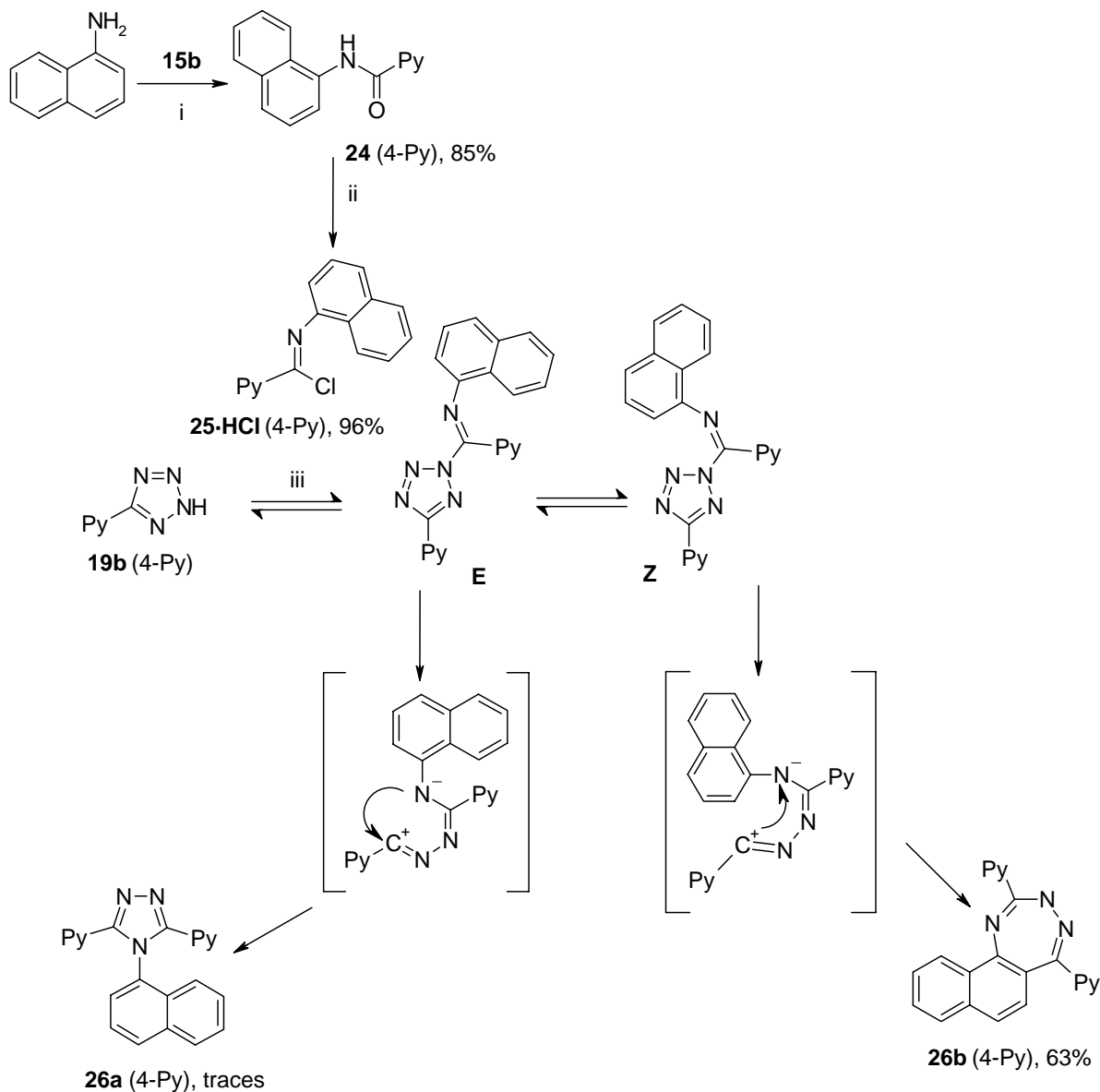
### Scheme 8

It should be emphasized, that in all cases of such rearrangements, no products of further transformation of  $\text{N}^1$ -acyl derivatives, such as 1,2,4-oxadiazole or *unsym*-triazole, were detected (Scheme 9).



### Scheme 9

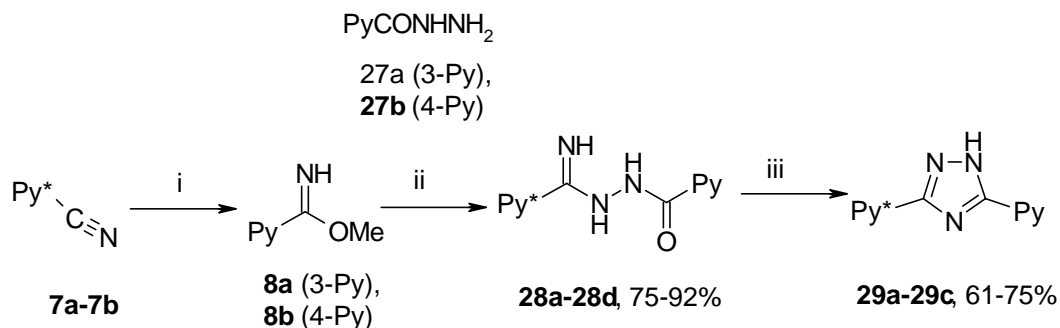
We also tested tetrazolyl-pyridines in the solvent-dependent reactions. It is known,<sup>26</sup> that (*Z*)- and (*E*)- $\text{N}^2$ -imidoyltetrazoles are labile, and can reversibly interconvert into each other. In our case (Scheme 10) in aprotic and less-polar toluene, the *Z*-form dominates and in the intermediate (shown in brackets), the cationic center attacks the electron-rich naphthalene ring resulting in the condensed 2,5-di(4-pyridyl)-3H-naphtho[1,2-*e*]-1,3,4-triazepine **26b**. Alternatively, triazole **26a** was registered as a trace by TLC control.



i – DMF, heat; ii –  $\text{PCl}_5$  reflux; iii –  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ , NaOH,  $\text{Et}_3\text{N}$ ; TEBAC; MePh, reflux.

### Scheme 10

For the synthesis of *unsym*-triazoles **29**, we applied the procedure depicted in Scheme 11. This approach is based on the preparation and isolation of the unsymmetrical amidrazones **28** with their consequent dehydration by heating.



i - MeONa, MeOH, rt; ii - MeOH, heat; 180 °C vacuum.

### Scheme 11

In summary, by the design of the reaction partners, we have developed a convenient and conceptually simple synthetic pathway to a family of novelazole bearing pyridines which are promising ligands for coordination chemistry.

## Experimental Section

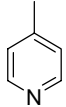
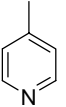







**General Procedures.** All starting materials were obtained commercially, unless otherwise stated, (Aldrich, Lancaster or Acros Organics) and all solvents were dried using literature procedures. TLC was performed using aluminium plates precoated with silica 60 F<sub>254</sub> (Merck) and visualized by iodine or UV light (254 nm). Column chromatography was carried out on silica gel (Fluka, particle size 0.040-0.063nm). The IR-spectra were recorded (nujole) on a Specord 75 IR instrument. NMR spectra were recorded in CDCl<sub>3</sub>, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a Jeol® “MS-D300” Spectrometer (EI, 70 eV), coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl-silicone) column. Elemental analyses data were obtained on a Carlo-Erba® ER-20 elemental analyzer. Melting points and boiling points were recorded at atmospheric pressure, unless otherwise stated, and are uncorrected.

### Typical procedure for the preparation of 3,5-diaryl-1H-pyrazoles

Hydrazine hydrate (15 mmol) in MeOH (20 ml) was added to a solution of the appropriate  $\beta$ -diketone<sup>9,27</sup> (10 mmol). The resulting mixture was stirred and refluxed for 2 h, and was then cooled and evaporated. The residue was crystallized from 2-propanol. The yields, melting points and spectral data of **2a-2c** are presented in Tables 1,2.



**Table 1.** Yields and spectral data of 3,5-diaryl-1*H*-pyrazoles **2a-2e**

	R1	R2	yield, %	m.p.(lit.) °C	IR (v, cm <sup>-1</sup> )	Ref
<b>2a</b>			95	251 (247-250)	3250 (NH)	27
<b>2b</b>			73	238 (231-232)	3240 (NH)	9
<b>2c</b>			51	221 (217-219)	3250 (NH)	9
<b>2d</b>		Ph	84	159	3240 (NH)	9
<b>2e</b>			77	142	3250 (NH)	9

**Table 2.** <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ ppm) data of 3,5-diaryl-1*H*-pyrazoles **2a-2c**. Structure–chemical shift correlations are available from the literature<sup>28,29,30</sup>

	Py(C <sup>2</sup> /C <sup>2'</sup> ) <sup>*</sup>	Py(C <sup>3</sup> /C <sup>3'</sup> )	Py(C <sup>4</sup> /C <sup>4'</sup> )	Py(C <sup>5</sup> /C <sup>5'</sup> )	Py(C <sup>6</sup> /C <sup>6'</sup> )	Pyraz (C <sup>3</sup> /C <sup>5</sup> )	Pyraz (C <sup>4</sup> )
<b>31</b>	150.2	122.3	-	122.3	150.2	148.4	110.5
<b>32</b>	150.5	-	135.9	124.1	150.9	147.6	108.2
<b>33</b>	150.2/-	122.5/121.2	-/136.9	122.5/123.1	150.2/151.5	148.9/148.6	113.2

\* the atoms of pyridine rings with lower locant number (2-pyridyl) were marked by apostrophes.

**3-Phenyl-5-(2-pyridyl)-1*H*-pyrazole (2d).** Yield 84%, colorless prismatic crystals. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, *J*, Hz): 8.70 (dd, 1H, 6H-Py, <sup>3</sup>*J*=4.5, <sup>4</sup>*J*=1.8), 7.90-7.88 (m, 2H, 2,6-H-Ph), 7.80 (dd, 1H, 3H-Py, <sup>3</sup>*J*=7.7, <sup>4</sup>*J*=1.8), 7.75 (dt, 1H, 4H-Py, <sup>3</sup>*J*=7.7, <sup>4</sup>*J*=1.8), 7.64-7.61 (m, 1H, 4H-Ph), 7.40 (dd, 1H, 5H-Py, <sup>3</sup>*J*=4.5, <sup>3</sup>*J*=7.7), 7.26-7.22 (m, 2H, 3,5-H-Ph), 7.12 (c, 1H, 4H-Pyraz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ, ppm): 151.3, 149.5, 148.8, 148.1, 137.2, 132.1, 129.0, 128.2, 125.4, 122.2, 121.3, 100.2. Anal. Calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.20; H, 4.92; N, 19.02.

**3-(2-Thienyl)-5-(2-pyridyl)-1*H*-pyrazole (2e).** Yield 77%, yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, *J*, Hz): 8.64 (d, 1H, 6H-Py, <sup>3</sup>*J*=4.5), 8.08 (d, 1H, 3H-Py, <sup>3</sup>*J*=7.0), 7.83 (d, 1H, 3H-Tf, <sup>3</sup>*J*=4.0), 7.72 (dt, 1H, 4H-Py, <sup>3</sup>*J*=7.0, <sup>4</sup>*J*=1.4), 7.60 (d, 1H, 5H-Tf, <sup>3</sup>*J*=5.0), 7.37 (dd, 1H, 5-HPy, <sup>3</sup>*J*=7.0, <sup>3</sup>*J*=4.5), 7.18 (dd, 1H, 4-HTf, <sup>3</sup>*J*=5.0, <sup>3</sup>*J*=4.0), 6.95 (c, 1H, 4H-Pyraz). <sup>13</sup>C NMR (CDCl<sub>3</sub>,

$\delta$ , ppm.): 151.0, 148.8, 143.4, 142.8, 140.6, 137.0, 135.1, 133.1, 124.2, 123.6, 121.1, 100.0. Anal. Calcd. for  $C_{12}H_9N_3S$ : C, 63.41; H, 3.99; N, 18.49. Found: C, 62.95; H, 3.73; N, 18.80.

**3,5-Di(3-pyridyl)isoxazole (3a).** An ethanol solution of 1,3-di(3-pyridyl)-1,3-propanedione (**1b**) (2.22 g, 10 mmol) was added to hydroxylamine (15 mmol) in ethanol. The mixture was stirred at 80 °C for 12 h, and was then cooled and evaporated. The residue was carefully extracted by dichloromethane (DCM, 3x20 ml), the organic phase was dried (sodium sulfate), and evaporated. The residue was crystallized from ethanol to yield 900 mg (41%) of oxazole **3a**, m.p. 202 °C, lit. 198 °C.<sup>9</sup>  $^{13}C$  NMR ( $CDCl_3$ ,  $\delta$ , ppm.): 164.2, 151.0, 150.8, 150.6, 150.5, 146.4, 136.2, 135.9, 124.9, 124.5, 97.4.

**(E/Z)-Tosylates of 3-acetylpyridine oxime (5a).** (*E/Z*)-3-Acetylpyridine oxime (**4a**) (10.3 g, 75 mmol) was dissolved in 36 ml of anhydrous pyridine, and the resulting mixture was ice-cooled. The reaction mixture was quenched by 15.7 g (82 mmol) of tosylchloride (TsCl) with vigorous stirring to keep the temperature below 5 °C. The mixture was kept overnight at 0 °C, and then poured onto 400 g of crushed ice. After slow crystallization of the initially formed yellow oil, the product was filtered, and crystallized from aqueous alcohol to give 9.9 g (41%) of beige crystals, m.p. 77-79 °C, lit. 78 °C.<sup>13</sup> The ratio (3:2) of *E*- and *Z*-isomers of **5a** was determined by  $^1H$  NMR.  $^1H$  NMR *Z*-5a ( $CDCl_3$ ,  $\delta$ , ppm, *J*, Hz): 2.38 (s, 3H,  $CH_3$ -Ts), 2.42 (s, 3H,  $CH_3$ -C=NOTs), 7.36 (d, 2H, 3,5-H-Ts,  $^3J=7.6$ ), 7.42 (ddd, 1H, 5H-Py,  $^3J=4.7$ ,  $^4J=1.8$ ), 7.78 (dt, 1H, 4H-Py,  $^3J=4.7$ ,  $^4J=1.8$ ), 7.86 (d, 2H, 2,6-H-Ts,  $^3J=7.6$ ), 8.60 (dd, 1H, 6H-Py,  $^3J=4.9$ ,  $^4J=1.8$ ), 8.68 (d, 1H, 2H-Py,  $^4J=1.8$ ).  $^1H$  NMR *E*5a ( $CDCl_3$ ,  $\delta$ , ppm, *J*, Hz): 2.37 (c, 3H,  $CH_3$ -Ts), 2.51 (c, 3H,  $CH_3$ -C=NOTs), 7.34 (ddd, 1H, 5H-Py,  $^3J=4.7$ ,  $^4J=1.8$ ), 7.39 (d, 2H, 3,5-H-Ts,  $^3J=7.5$ ), 7.90 (dt, 1H, 4H-Py,  $^3J=4.7$ ,  $^4J=1.8$ ), 7.94 (d, 2H, 2,6-H-Ts,  $^3J=7.5$ ), 8.65 (dd, 1H, 6H-Py,  $^3J=4.9$ ,  $^4J=1.8$ ), 8.82 (d, 1H, 2H-Py,  $^4J=1.8$ ).

**(E)-Tosylate of 4-acetylpyridine oxime (5b).** In a similar manner from 8.20 g (60 mmol) of (*E*)-4-acetylpyridine oxime **4b** and 12.4 g (65 mmol) of TsCl 15.65 g (90%) of **5b** was obtained, m.p. 81 °C, lit. 81 °C.<sup>4</sup>  $^1H$  NMR ( $CDCl_3$ ,  $\delta$ , ppm, *J*, Hz): 2.38 (s, 3H,  $CH_3$ -Ts), 2.53 (s, 3H,  $CH_3$ -C=NOTs), 7.40 (d, 2H, 3,5-H-Ts,  $^3J=7.5$ ), 7.95 (d, 2H, 2,6-H-Ts,  $^3J=7.5$ ), 8.08 (d, 2H, 3,5H-Py,  $^3J=6.7$ ), 9.02 (d, 2H, 2,6-H-Py,  $^4J=6.7$ ).

**2-Amino-1-(3-pyridyl)ethanone (6a).** The reaction was carried out under an argon atmosphere. Potassium (1.5 g, 38 mmol) was cautiously dissolved in 25 ml of dry ether. (*E/Z*)-Tosylates of 3-acetylpyridine oxime **5a** (9.9 g, 34 mmol) was then added to this solution. The resulting mixture was stirred at room temperature for 1 h. The resulting red-colored solution was filtered from sodium tosylate, and quenched by 600 ml of dry ether. The sodium tosylate formed once again was filtered. The product was collected after ethereal phase extraction (3x25 ml 2N HCl), followed by evaporation of the water phase (temperature should not exceed 40 °C). Crystallization from absolute alcohol gave 3.2 g (45%) of white crystals of the dihydrochloride, m.p. 172 °C (dec.), lit. 172 °C (dec.).<sup>13</sup> This compound was sensitive to moisture and air.  $^1H$  NMR ( $CDCl_3$ ,  $\delta$ , ppm, *J*, Hz): 3.55 (m, 2H,  $CH_2-NH_3^+$ ), 6.58 (br.t, 3H,  $NH_3^+$ ), 7.48 (m, 1H, 5H-Py), 8.05 (d, 1H, 4H-Py,  $^3J=7.5$ ), 8.71 (d, 1H, 6H-Py,  $^3J=4.8$ ), 9.12 (s, 1H, 2H-Py), 11.21 (br.s, 1H,  $NH^+$ -Py). IR: 3450 (NH,  $NH_3$ ); 1690 (C=O).

**2-Amino-1-(4-pyridyl)ethanone (6b).** In a similar manner from 14.5 g (50 mmol) of **5b** and 2.15 g (55 mmol) of potassium **6b** was obtained as colorless needles. Yield 4.72g (45%), m.p. 192-228°C (dec.), lit. 230-235 °C (dec.).<sup>31</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, J, Hz): 3.55 (m, 2H, CH<sub>2</sub>-NH<sub>3</sub><sup>+</sup>), 6.65 (br.t, 3H, NH<sub>3</sub><sup>+</sup>), 7.42 (d, 2H, 3,5-H-Py, <sup>3</sup>J=5.0), 8.60 (d, 2H, 2,6H-Py, <sup>3</sup>J=5.0), 11.05 (br.s, 1H, NH<sup>+</sup>-Py). IR: 3450 (NH, NH<sub>3</sub>); 1690 (C=O).

#### Typical procedure for the preparation of 2,4-dipyridyl-1H-imidazoles 9a-9d

The methanol solution (25 ml, 0.5 M) of appropriate methyl pyridylcarbimide<sup>7</sup> was quenched by acetic acid up to a neutral pH. To this mixture, 2-amino-1-pyridylethanone dihydrochloride (2.6 g, 12.5 mmol) was added. The resulting mixture was stirred for 1 h, and then refluxed for 2 h. Then it was cooled, and evaporated to dryness. The residue was dissolved in a 10% sodium hydroxide solution so that the pH stayed near 10, and this solution was extracted by DCM (3×10 ml). The organic phase was dried and evaporated, the residue was then crystallized from chloroform and acetone (to remove ammonia chloride). The yields, melting points and spectral data of **9a-9d** are presented in Tables 3,4.

**Table 3.** Yields and spectral data of 2,4-dipyridyl-1H-imidazoles **9a-9d**

Starting materials	Color	Yield, %	m.p. °C	IR (ν, cm <sup>-1</sup> ):	Found: Anal. Calcd. for C <sub>13</sub> H <sub>10</sub> N <sub>4</sub>		
					C	H	N
<b>9a</b> <b>6a+8a</b>	light-yellow	38	169	3300 (NH)	70.25	4.54	25.21
<b>9b</b> <b>6a+8b</b>	light-yellow	56	183	3300 (NH)	69.82	4.12	25.39
<b>9c</b> <b>6b+8a</b>	colorless	54	192	3300 (NH)	69.75	4.01	25.74
<b>9d</b> <b>6b+8b</b>	colorless	70	209	3300 (NH)	69.87	4.53	25.11
					70.12	4.38	24.98

**Table 4.** <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ ppm, J Hz), <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ ppm) data of 2,4-dipyridyl-1H-imidazoles **9a-9d** Structure –chemical shift correlations were reported in the literature.<sup>32</sup> See supporting info. Page 241

#### Typical procedure for the preparation of 2,4-dipyridylthiazoles 12a-12d<sup>33</sup>

2-Bromo-1-pyridinylethanone (**10a** or **10b**) (2.81 g, 10 mmol), pyridylcarbothioamide (**11a** or **11b**) (1.38 g, 10mmol) and 50 ml of absolute ethanol were mixed in a 100 ml round-bottom flask. The resulting mixture was refluxed for 2h, then cooled and filtered. Triethylamine (2.5 ml, 20 mmol)) and isopropanol (30 ml) were added to the resulting solid, and the reaction mixture

was brought to reflux for 30 min. After cooling and evaporation, the residue was quenched with 10 ml of water and was extracted by DCM (3x30 ml). The organic phase was dried, evaporated and the rest was crystallized from 2-propanol to give the appropriate thiazoles. The yields, melting points and spectral data of **12a-12d** are presented in Tables 5,6.

**Table 5.** Yields and spectral data of 2,4-dipyridylthiazoles **12a-12d**

	Starting materials	Color	Yield, %	m.p. °C	Found:		
					Anal. Calcd. for C <sub>13</sub> H <sub>9</sub> N <sub>3</sub> S		
					C	H	N
					65.25	3.79	17.56
<b>12a</b>	<b>10a+11a</b>	beige	33	134	65.12	4.02	18.01
<b>12b</b>	<b>10a+11b</b>	beige	31	160	65.54	4.05	17.70
<b>12c</b>	<b>10b+11a</b>	beige	39	122	65.19	3.53	17.18
<b>12d</b>	<b>10b+11b</b>	beige	25	171	65.10	3.38	17.08

**Table 6.** <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ ppm, J Hz), <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ ppm) data of 2,4-dipyridylthiazoles **12a-12d**. Structure –chemical shift correlations were reported in the literature.<sup>34</sup> See supporting info. Page 242

### 2,5-Di(4-pyridyl)oxazole (**14**)

**N-Isonicotinoyl-2-amino-1-(4-pyridyl)ethanone (13).** Isonicotinoyl chloride (420 mg, 2 mmol) was added to an ice-cooled 2-aminoethanone (**6b**) (380 mg, 2.1 mmol) solution in DMF (10 ml). The resulting mixture was allowed to warm to r.t., and was then stirred for 6 h. The final mixture was evaporated to half of the volume at oil-pump vacuum, and was then quenched by water to give a solid, which was filtered and crystallized from ethanol. Yield 230 mg (52%), beige solid, m.p. 126 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, J, Hz): 3.73 (d, 2H, CH<sub>2</sub>-NHCO, <sup>3</sup>J=6.2), 6.65 (br.t, 3H, NH<sub>3</sub><sup>+</sup>), 7.75-7.80 (m, 4H, 3,5-H-Py<sup>12</sup>), 8.95-9.01 (m, 4H, 2,6H-Py<sup>12</sup>), 10.50 (br.s, 1H, NHCOPy). IR: 3380 (CONH); 1700, 1690 (C=O). MS (m/z, %): 241(M+, 12), 106(PyCO, 100). Amidoketone **13** (240 mg, 1mmol) was heated for 15 min to 170-180 °C on a Wood-bath. After cooling, the residue was quenched by ethanol, and was evaporated. The purification of solid by column chromatography (CHCl<sub>3</sub>-MeOH 15:1) furnished 65 mg (28%) of starting **13** and 14 mg (6%) of oxazole **14** as pale-yellow needles, m.p. 175 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, J, Hz): 7.55 (d, 2H, 3,5H-Py<sup>5</sup>, <sup>3</sup>J=5.5), 7.65 (s, 3H, 4H-Oxaz), 7.86 (d, 2H, 3,5-H-Py<sup>5</sup>, <sup>3</sup>J=5.5), 8.65 (d, 2H,

2,6H-Py<sup>2</sup>, <sup>3</sup>J=5.5), 8.78 (d, 2H, 2,6H-Py<sup>2</sup>, <sup>3</sup>J=5.5). IR (neat): 2950 (CH); 1580 (Py). MS (m/z, %): 223(M+, 12), 78 (Py, 100).

**Typical procedure for the preparation of O-pyridoyl pyridinecarbamidoxime 17a-17d**<sup>11</sup>  
Well-grind potassium carbonate (4.3 g, 30 mmol) was added to a solution of pyridinecarbamidoxime (2.75g, 20 mmol) in dry acetone. The appropriate pyridoyl chloride (3.60 g, 20 mmol) was then added in a few portions. The resulting mixture was stirred overnight at r.t., then evaporated to dryness, and quenched with 30 ml of water. This solution was extracted by DCM (2×50 ml), the organic phase was dried, evaporated and crystallized from aqueous alcohol to give O-acylated amidoximes **17**. The yields, melting points and spectral data of **17a-17d** are presented in Table 7.

**Table 7.** Yields and spectral data of O-pyridoyl pyridinecarbamidoxime **17a-17d**

	Starting materials	Yield, %	m.p. °C (dec.)	IR (ν, cm <sup>-1</sup> ):	<sup>1</sup> H NMR(DMSO-d <sub>6</sub> , δ ppm)
<b>17a</b>	<b>15a+16a</b>	76	192	3150 (NH,NH <sub>2</sub> ), 1710(COO)	9.9(br.s., 2H), 9.2(m, 2H), 8.82(m, 2H), 8.29(1H), 8.10(1H), 7.48 (1H), 7.41(1H)
<b>17b</b>	<b>15a+16b</b>	82	197	3150 (NH,NH <sub>2</sub> ), 1710(COO)	9.7(br.s., 2H), 9.1(s, 1H), 8.82(d, 2H), 8.68(1H), 8.32(1H), 8.05 (1H), 7.62 (d, 2H), 7.40(1H)
<b>17c</b>	<b>15b+16a</b>	74	193	3150 (NH,NH <sub>2</sub> ), 1710(COO)	9.8(br.s., 2H), 9.1(s, 1H), 8.88 (d, 2H), 8.72(1H), 8.16(1H), 7.70 (d, 2H), 7.28(1H)
<b>17d</b>	<b>15b+16b</b>	79	203	3150 (NH,NH <sub>2</sub> ), 1710(COO)	9.8(br.s., 2H), 8.9-8.8(m, 4H), 7.68 (d, 2H), 7.61(d, 2H)

**Typical procedure for the preparation of 3,5-dipyridyl-1,2,4-oxadiazoles 18a-18d**

A slurry of the appropriate O-pyridoyl pyridinecarbamidoxime **14** (3g, 12.4 mmol) in 50 ml of dry toluene was refluxed with a Dean-Stark's trap for 4-6h (TLC control). After cooling, the mixture was evaporated to dryness, and the residue was crystallized from methanol. The yields, melting points and elemental composition data of **18a-18d** are presented in Tables 8,9.

**Table 8.** Yields and physical data of **3,5-dipyridyl-1,2,4-oxadiazoles 18a-18d**

Starting materials	Yield, %	m.p. °C	Found:			
			Anal. Calcd. for			
			C <sub>12</sub> H <sub>8</sub> N <sub>4</sub> O			
			C	H	N	
			65.28	3.60	24.99	
<b>18a</b>	<b>17a</b>	91	169	65.70	3.32	24.41
<b>18b</b>	<b>17b</b>	85	176	64.93	3.71	24.22
<b>18c</b>	<b>17c</b>	80	170	65.55	3.60	25.13
<b>18d</b>	<b>17d</b>	80	185	65.30	3.47	24.78

**Table 9.** <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ ppm, J Hz), <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ ppm) data of **3,5-dipyridyl-1,2,4-oxadiazoles 18a-18d**. See supporting info. Page 243

**Preparation of 2,5-dipyridyl-1,3,4-oxadiazoles 20a-20c.**<sup>25</sup> Pyridoyl chloride hydrochloride (1.8g, 10 mmol) was added to a well-stirred solution of 5-pyridyltetrazole (1.5 g, 10 mmol) in 15 ml of dry pyridine, preheated to 50 °C. The resulting yellow mixture was cautiously heated to 75-90 °C and kept at this temperature until the nitrogen gas evolution ceased. Then the mixture was cooled and filtered. The free base was isolated by consequent quenching with NaOH using a minimum water volume, extraction by DCM (3x30 ml), evaporation and crystallization from ethanol.

Under microwave activation, both reagents (2 mmol each) in 5 ml pyridine were used. Irradiation was carried out in domestic MW-oven at 800 W power-level for 30 s period. The yields, melting points and elemental composition data of **20a-20c** are presented in Tables 10,11.

**Table 10.** Yields, melting points and elemental composition data of **2,5-dipyridyl-1,3,4-oxadiazoles 20a-20c**

	Starting materials	Yield, % heating/ MW <sub>irr</sub>	m.p. °C	m.p. °C (lit. <sup>24</sup> ) 20·HCl	Found:		
					Anal. Calcd. for C <sub>12</sub> H <sub>8</sub> N <sub>4</sub> O		
					C	H	N
					65.28	3.60	24.99
<b>20a</b>	<b>19a+15a</b>	70/78	180	239 (225)	65.20	4.05	25.06
<b>20b</b>	<b>19a+15b</b>	72/83	184	229 (221)	65.31	3.88	24.79
	<b>19b+15a</b>	88/90	184				
<b>20c</b>	<b>19b+15b</b>	86/87	188	251 (250)	65.29	3.63	25.08

**Table 11.** <sup>1</sup>H NMR(CDCl<sub>3</sub>, δ ppm, J Hz), <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ ppm) data of **2,5-dipyridyl-1,3,4-oxadiazoles 20a-20c**. See supporting info. Page 244

**3,5-Di(4-pyridyl)-4-(4-bromophenyl)-1,2,4-triazole (23).** *N*-(4-Bromophenyl)isonicotinamide (**21**). The mixture of isonicotinoyl chloride hydrochloride (3.6g, 21mmol) and 4-bromoaniline (3.45g, 20mmol) in 30 ml of dry DMF was heated at 75 °C over 30 min. Then, the reaction mixture was poured onto 250 g of crushed ice and filtered. After recrystallization from alcohol 4.5 g (80%), a white solid was isolated, m.p. 214 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, J, Hz): 7.40 (d, 2H, 3,5-H-Ph, <sup>3</sup>J=7.8), 7.65 (d, 2H, 2,6-H-Ph, <sup>3</sup>J=7.8), 7.75 (d, 2H, 3,5-H-Py, <sup>3</sup>J=6.1), 8.85 (d, 2H, 2,6H-Py, <sup>3</sup>J=6.1), 11.30 (br.s, 1H, NHCOPY). IR: 3320 (CONH); 1700 (C=O).

*N*-(4-Bromophenyl)-pyridin-4-yl-carbimidoyl chloride (**22**). Well-grind phosphorus pentachloride (2.30 g, 11 mmol) was added to the slurry solution of amide **21** (2.77 g, 10 mmol) in 20 ml of dry toluene. The reaction mixture was heated on a boiling water-bath for 2 h, then allowed to cool, and evaporated to dryness. The residue (3.2 g, 96%) was washed with ether, vacuum-dried and resulted in a yellow solid, m.p. 162-168 °C (dec.), and was used immediately. The appropriate triazole was synthesized in similar manner from 5-(4-pyridyl)-1*H*-tetrazole (**19b**) (1.40 g, 9.5 mmol) and **22** (3.15 g, 9.5 mmol). Pure product was isolated by column chromatography (CHCl<sub>3</sub>-MeOH 15:1) to give 2.08 g (59%) of yellow solid, m.p. 284 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ, ppm, J, Hz): 7.45 (d, 2H, 3,5-H-Ph, <sup>3</sup>J=7.5), 7.68 (d, 2H, 2,6-H-Ph, <sup>3</sup>J=7.5), 8.05 (d, 2H, 3,5-H-Py, <sup>3</sup>J=6.3), 8.72 (d, 4H, 2,6H-Py, <sup>3</sup>J=6.3). IR: 3320 (CONH); 1700 (C=O). <sup>13</sup>C NMR(CDCl<sub>3</sub>, δ, ppm,): 152.4, 147.1, 143.7, 136.0, 134.6, 124.2, 120.5, 119.1. Anal. Calcd. for C<sub>18</sub>H<sub>12</sub>N<sub>5</sub>Br: C, 57.16; H, 3.20; N, 18.52. Found: C, 57.90; H, 3.68; N, 18.81.

**2,5-Di(4-pyridyl)-3*H*-naphtho[1,2-*e*]-1,3,4-triazepine (26b)**

*N*-(1-Naphthyl)isonicotinamide (**24**) was obtained in a similar manner from 1-naphthylamine (2.85 g, 20 mmol) and isonicotinoyl chloride hydrochloride (3.6 g, 21 mmol) as colorless needles. Yield 4.2 g (85%), m.p. 235 °C (EtOH), lit. m.p. 233 - 234 °C<sup>35</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ,

ppm, J, Hz): 6.94-7.34 (4H, H-Naph), 7.65 (m, 1H, H-Naph), 7.70 (d, 2H, 3,5-H-Py,  $^3J=6.2$ ), 7.95 (m, 1H, H-Naph), 8.42 (m, 1H, H-Naph), 8.80 (d, 2H, 2,6H-Py,  $^3J=6.2$ ), 11.05 (br.s, 1H, NHCOPY). IR: 3320 (CONH); 1700 (C=O).

**N-(1-Naphthyl)-pyridin-4-yl-carbimidoyl chloride hydrochloride (25)** was obtained in the same way from **24** (2.5 g, 10 mmol) and  $\text{PCl}_5$  (2.30 g, 11 mmol) as a yellow solid. Yield 2.92 g (96%), m.p. 170-175 °C (dec.). The compound was used without further characterization.

**2,5-Di(4-pyridyl)-3H-naphtho[1,2-e]-1,3,4-triazepine (26b)**. 10 ml of a water solution of NaOH (900 mg) was added to a slurry of 5-(4-pyridyl)-*1H*-tetrazole (**19b**) (1.40 g, 9.5 mmol) in 10 ml of water. To this solution the solution of hydrochloride **25** (2.90 g, 9.5 mmol) in 30 ml of DCM, containing 1.2 ml triethylamine and 50 mg TEBAC, was added. The resulting mixture was then intensively stirred for 1 h. The organic layer was separated and the aqueous layer was extracted by 10 ml of DCM. The organic phases were combined and evaporated. The crude oily 2-(N-arylimidoil)tetrazole was placed in 20 ml of dry toluene, and was heated at 90-100 °C for 1 h. After cooling the reaction mixture was filtered and evaporated to dryness. The residue was crystallized from a benzene-ethyl acetate mixture to give triazepine **26** as brown solid. Yield 2.02 g (63%), m.p. 228-231 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm, J, Hz): 7.45 (m, 2H, 4,6-H-Naph), 7.60 (d, 2H, 3,5-H-Py,  $^3J=6.0$ ), 7.81 (m, 2H, 3,7-H-Naph), 7.96-7.98 (2H, 5,8-H-Naph), 8.19 (d, 2H, 3,5-H-Py,  $^3J=6.0$ ), 8.69 (d, 2H, 2,6H-Py,  $^3J=6.0$ ), 8.84 (d, 2H, 2,6H-Py,  $^3J=6.0$ ), 10.30 (br.s, 1H, NH). IR: 3405 (NH); 1575 (Py). Anal. Calcd. for  $\text{C}_{22}\text{H}_{15}\text{N}_5$  C, 75.63; H, 4.33; N, 20.04. Found: C, 75.36; H, 3.89; N, 20.75.

**3,5-Dipyridyl-1H-1,2,4-triazoles 29a-29c** were synthesized according to the literature data<sup>17</sup> in two steps via cyclocondensation of methyl pyridinecarbimidates with the appropriate pyridoylhydrazine. The spectral data of **20a-20c** are presented in Table 12.

**Table 12.**  $^1\text{H}$  NMR( $\text{CDCl}_3$ ,  $\delta$  ppm, J Hz),  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ ,  $\delta$  ppm) data of **3,5-Dipyridyl-1H-1,2,4-triazoles 27a-27c**. See supporting info. Page 245

## [Supplementary information is Available](#)

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