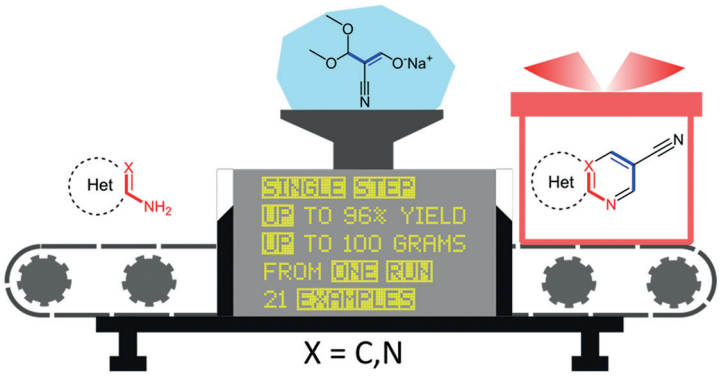
Synthesis A. P. Mityuk et al. Paper

Efficient Route for the Synthesis of Diverse Heteroannelated 5-Cyanopyridines

Andrey P. Mityuk[a]
Andrii Hrebonkin[a]
Pavlo S. Lebed[a,b]
Galyna P. Grabchuk[b]
Dmitriy M. Volochnyuk*[a,b,c]
Sergey V. Ryabukhin*[a,b]

[a] Enamine Ltd., 78 Chervonotkatska str., Kyiv, Ukraine
s.v.ryabukhin@gmail.com
d.volochnyuk@gmail.com
[b] Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., Kyiv, Ukraine
[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska str., Kyiv, Ukraine



Received: 21.09.2020
Accepted after revision: 18.01.2021
Published online: 18.01.2021
DOI: 10.1055/a-1360-9852; Art ID: ss-2020-t0627-op

Abstract The new efficient, convenient protocol for the synthesis of heteroannelated 3-cyanopyridines and pyrimidines starting from diverse aminoheterocycles and 3,3-dimethoxy-2-formylpropionitrile sodium salt was elaborated. The advantages and improvements of the procedure compared to previously known methods are shown. The scope and limitations of the method are determined. The impact of the structural features on regioselectivity are discussed. The preparativeness, scalability, and application scope of the elaborated protocol are demonstrated by the synthesis of five heteroannelated 3-cyanopyridines in quantities up to 100 grams.

Key words aminoheterocycles, heterocyclization, heteroannelated 3-cyanopyridines, heteroannelated 3-cyanopyrimidines, 2-dimethoxy-3-hydroxyacrylonitrile

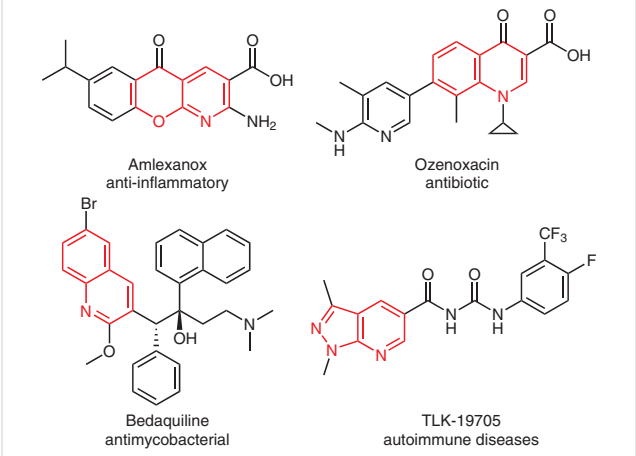


Figure 1 Examples of bioactive fused pyridines

Fused pyridines find application in various fields of medicinal and agrochemistry.[1] In recent years, researchers from all over the world have claimed biological activity of such compounds. The scope of their utilization is very wide. The mentioned compounds have been used as anti-inflammatory,[5] antiallergic,[2] antidiabetic,[3] antimicrobial,[4] and anticancer[5] agents. In most cases, examples of fused pyridines for successful application in the pointed fields were represented by species with the quinoline and imidazo[1,2-*a*]-pyridine cores (Figure 1). Other heteroannelated pyridine cores can also possess high biological activity, but scarce studies thereof can be explained, in particular, by the limited access to their functionalized derivatives.

Therefore, fused pyridines with different annelated heterocycles have drawn our attention. In our ongoing efforts towards in-house medicinal-chemistry-relevant building-block-collection enhancement in a cost-effective and lab-friendly manner,[6] heteroannelated 5-cyanopyridines were selected as the target products of the research. Such a selection could be explained by a lot of options to transform the cyano group into other function,[7] as well as the potential to introduce heteroannelated pyridine cores into promising biologically active scaffolds as substituents using the common reactions of nitriles.[8]

Nowadays, various methods were proposed for the synthesis of 5-functionalized heteroaryl[*b*]pyridines. Such methods can be divided into three groups: the pyridine ring has been built on the other heterocyclic core; the additional heterocyclic ring has been constructed on a pyridine ring; the substrates, obtained in the two previous ways, have been modified.

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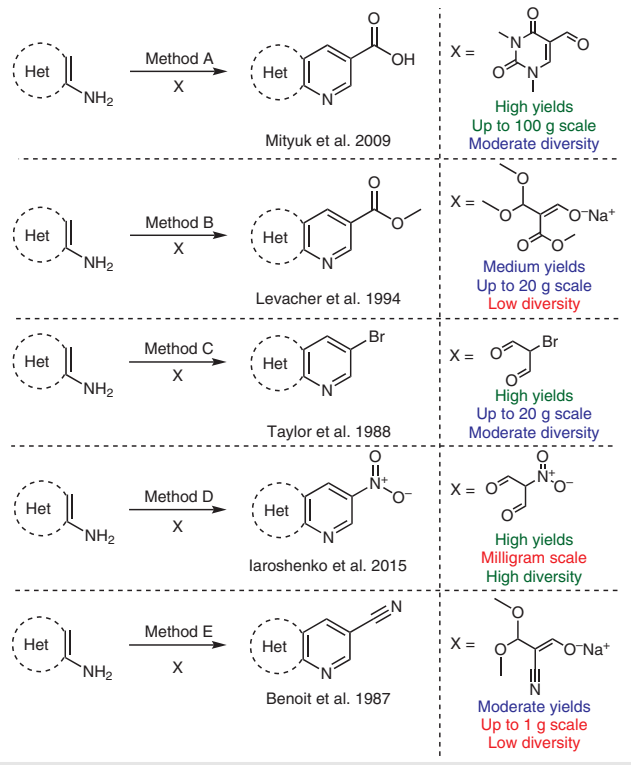
The first group almost fully consists of the condensations of (hetero)arylamines and 1,3-binucleophilic reagents. A wide arsenal of different reagents used as 1,3-binuclephiles ensures a very huge diversity of the function in the 5-position.[9] Previously, we reported the introduction of the carboxylic function by the cyclization of (hetero)aromatic amines with 5-formyluracil followed by the hydrolysis of the urea obtained.[10] To prepare esters in a one-pot manner, sodium 2-(dimethoxymethyl)-3-ethoxy-3-oxoprop-1-en-1-olate was proposed.[11] This approach is an ideological extension of the use of sodium 2-cyano-3,3-dimethoxyprop-1-en-1-olate for the synthesis of heteroaryl[3,4-*b*]pyridines with cyano group in the fifth position.[12] For 5-nitro- and 5-bromo-substituted representatives, a method was developed based on the use of nitro-[13] and bromomalonealdehyde.[14] All these methods are summarized in Scheme 1.



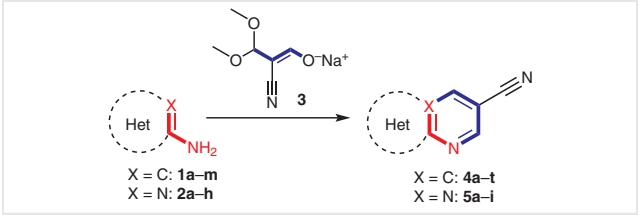
Scheme 1 The literature data for the synthesis of 5-functionalized heteroannelated pyridines

The second group does not have so many representatives as the first one. The poor variety of substituents at the 5th position is the main characteristic of this group. We found that only alkyl- and halogen-substituted derivatives were obtained by this route,[15] unlike the diversity of the first-group compounds. Another problem to use this strategy for increasing the chemical space of new cores is the fact that it does not lead to form new unique combinations of pyridine and heteroaromatic cycle. This group of methods is acceptable for obtaining new compounds with conventional core, but not to obtain new scaffolds.

The third group contains well-known transformations like C–C couplings (acetylene, alkene, or aryl addition), reduction of acetylene, hydrolysis of nitriles, synthesis of amides from carboxylic acids, amines from nitro-substituted compounds. This group was not considered in our research, since our aim was to develop a new procedure for pyridine ring assembling.

Earlier we have shown that cyclization of the hetarylamines with 1,3-binucleophilic reagents led to different derivatives of hetarylpyridines.[10] From the other hand, we developed the method for preparation of acids which allowed us to produce various potential building blocks.[10a] Unfortunately, the flaw of this method was the scale limitations. So, we decided to develop new methods or to optimize old ones for obtaining new types of building blocks based on heteroannelated pyridines. Nitriles were selected as the substrates because such compounds can be easily turned out into substances with maximum diversity of functional groups – amines, ketones, acids, esters, amides, amidines, etc.

As the starting point of our research, we have taken the original procedure of Benoit and co-workers, who described the synthesis of pyrrolo-, thiopheno-, and pyrazolopyridines based on the reaction of aminoheterocycles **1** with 3,3-dimethoxy-2-formylpropionitrile sodium salt **3** (Scheme 2). Unfortunately, the information in this paper was too fragmentary, the scales were small, and the scope was not determined. Our objective was to introduce a large number of diverse aminoheterocycles in this reaction (Figure 2). Moreover, we decided to expand this reaction on the formation of pyrimidines by the replacement of α-CH-aminoheterocycle **1** to α-NH analogue **2**. So, the additional optimization and scope determination were needed.



Scheme 2 General scheme for the synthesis of heteroannelated pyridines **4** and pyrimidines **5**

First of all, we decided to decrease the temperature of the reaction mixture and HCl concentration to avoid the decomposition of heterocycles, which were unstable in harsh acidic conditions. The idea was that such changes would allow us to expand the scope of the reaction to less stable heterocycles than thiophene, pyrazole, and pyrrole with

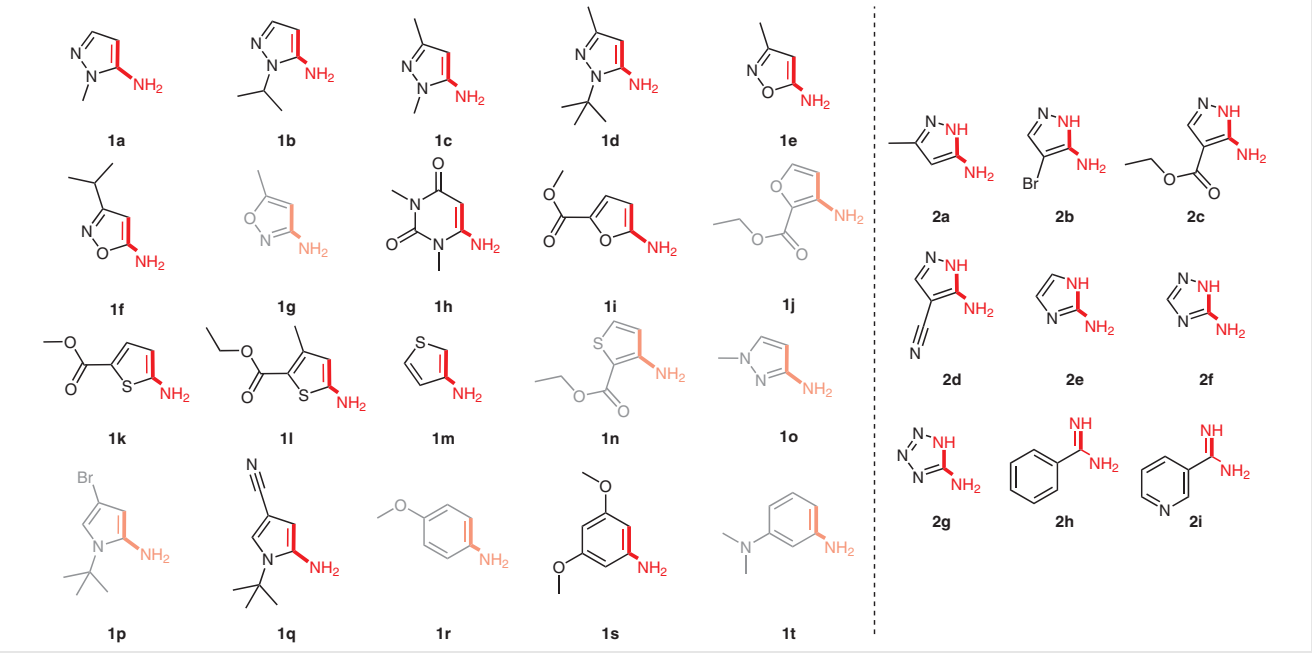


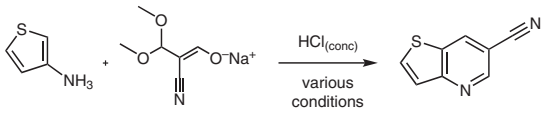
Figure 2 The set of substrates **1a–t** and **2a–i** used to determine the scope of amine condensation with sodium salt of 2-dimethoxy-3-hydroxyacrylonitrile

stabilizing acceptor substituents. The next step was the optimization of the solvent and its quantity to generate more soft reaction conditions. The reaction time and reagents ratio were then also optimized (Table 1).

As we can see from Table 1, the reaction took place at room temperature, and the temperature increase is not needed (entry 2). The optimal reaction time was 24 hours (entry 8). The longer reaction time did not result in a significant increase in the product yield (entry 9). It was found that alcohols were the best solvents (entries 10–12). We chose MeOH (entries 10–14) for further studies due to the higher solubility of the compound in it. Also, in our opinion, MeOH had good outlooks for scale-up. Amounts of MeOH and HCl were also minimized to increase the scale-up prospects (entries 17 and 22). Finally, the optimal reagents ratio, i.e., 20% excess of the salt **3**, was found. The validated conditions were 1 mmol of starting aminoheterocycle **1** in 4 mL of MeOH, 1.2 mmol of **3**, 0.4 mL of HCl, room temperature, 24 hours. Under these conditions, the yield of the model aminothiophene **1m** was 93% with an isolated yield of 87% after the neutralization of the reaction mixture by a saturated solution of $NaHCO_3$ to pH 7–8, extraction by $CHCl_3$, evaporation and preparative liquid gradient chromatography (10% EtOAc in hexane).

On the next stage, the aminoheterocycles **1a–t** and **2a–i** were tested in the elaborated procedure (Table 2). The aminopyrazoles **1a–d**, aminouracile **1h**, and aminothiophenes **1k–m** showed excellent results with high yields of the final products (>85%) in the reaction mixture and high preparative yields (78–94%). Introduction of a strong electron-accepting group into the aminopyrrole ring (**1q**) adhered the reaction, the product yield was also high. On the other hand, the reaction between 3,3-dimethoxy-2-formylpropionitrile sodium salt **3** and compounds more sensitive to acids like aminoisoxazoles **1e**,**f** and aminofurane **1i** passed not so efficiently. The yields in the reaction mixture was lower (68–78%), and the target compounds formed with moderate preparative yields (61–74%). In the case of aminoisoxazole **1g** and aminopyrrole **1p** the products were detected only in trace amounts in the reaction mixture. Thus, it can be concluded that the reaction does not occur upon the decrease in substrates stability towards acids. We also found that aminoheterocycles **1j**,**n**,**o** did not react with **3** under optimized conditions; this observation can be explained by the lower activity of α-C–H. Aromatic amines also could be the substrates of the reaction. The same principles of scope determination were acceptable for them. From the tested anilines, **1s** was similar to the thiophenes **1k–m** and could form the benzannelated pyridine **4s** in a 92% yield. Instead, the reaction did not take place with **1r** and **1t** as the substrates. The reason was that **1r** has only one additional π-donating group (OMe). Moreover, it is located in the *para* position to amine unlike to **1s** (two OMe groups in *meta* positions). In this case, the donating effect on α-CH in **1r** is much lower, and the activity to electrophilic substitution is less. From the other side, the activity of α-CH in compound **1t** is enough but the instability of the latter under the acidic conditions occurred.

Table 1 Optimization Protocols on the Model Substrate **1m**

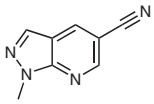
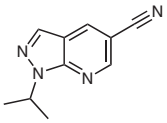
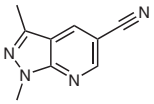
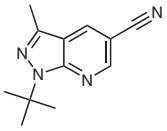
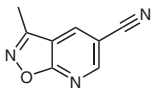
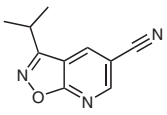
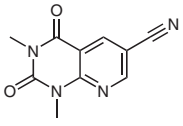
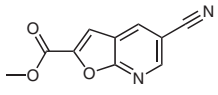
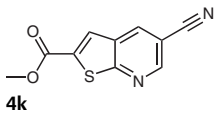
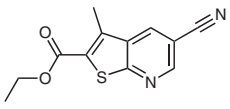


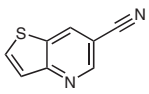
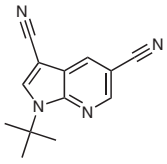
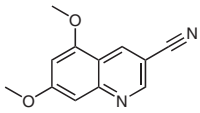
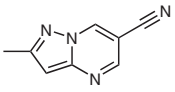
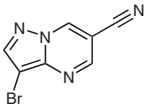
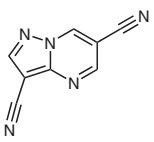
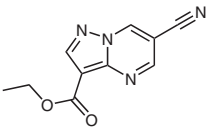
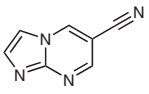
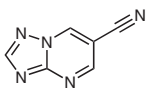
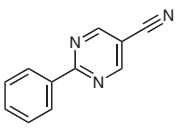
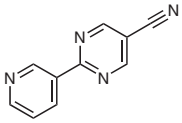
1m **3** **4m**

Temperature			
Entry	Conditions	Temp (°C)	Yield (%)[a]
1	**1m** (1 mmol), **3** (1.2 mmol), HCl (0.4 mL), MeOH (2 mL), 8 h	0	44
2		rt (ca. 25)	76
3		40	74
4		65	67
Time			
Entry	Conditions	Time (h)	Yield (%)[a]
5	**1m** (1 mmol), **3** (1.2 mmol), HCl (0.4 mL), MeOH (2 mL), r.t.	4	57
6		8	76
7		12	82
8		24	86
9		48	87
Solvent			
Entry	Conditions	Solvent	Yield (%)[a]
10	**1m** (1 mmol), **3** (1.2 mmol), HCl (0.4 mL), solvent (2 mL), r.t., 24 h	MeOH	86
11		EtOH	85
12		*i*-PrOH	82
13		MeCN	64
14		dioxane	78
Amount of solvent (mL for 1 mmol)			
Entry	Conditions	Value (mL)	Yield (%)[a]
15	**1m** (1 mmol), **3** (1.2 mmol), HCl (0.4 mL), MeOH, r.t., 24 h	1	76
16		2	85
17		4	93
18		6	93
19		8	91
20		10	89
Amount of HCl (mL of 35% solution for mmol)			
Entry	Conditions	Value (mL)	Yield (%)[a]
21	**1m** (1 mmol), **3**, HCl (0.4 mL), MeOH (4 mL), r.t., 24 h	0.2	72
22		0.4	93
23		0.6	94
24		0.8	91
25		1.0	88
Reagent ratio (**1m**/**3**)			
Entry	Conditions	Ratio (mmol)	Yield (%)[a]
26	**1m**, **3**, HCl (0.4 mL), MeOH (4 mL), r.t., 24 h	1:0,8	64
27		1:1	82
28		1:1.1	92
29		1:1.2	93
30		1:1.4	92
31		1:1.8	85

[a] Yield was determined by LCMS of quenched reaction mixture.

Table 2 Yields, Melting Points, and MS Data of Products **4** and **5**

Starting material	Product	MS *m/z* [M + 1]	Yield (g, %)[a]	Mp (°C)
1a	 **4a**	159.2	0.69, 87 (65.6, 83)[b]	172
1b	 **4b**	187.2	0.77, 83	89
1c	 **4c**	173.2	0.81, 94	144
1d	 **4d**	215.2	0.92, 86	134–152[c]
1e	 **4e**	160.2	0.49, 61	125
1f	 **4f**	188.2	0.69, 74	67
1h	 **4h**	217.0	0.94, 87 (98.4, 91)[b]	167
1i	 **4i**	203.2	0.65, 64	162
1k	 **4k**	219.0	0.85, 78 (82.9, 76)[b]	168
1l	 **4l**	247.1	1.06, 86	175–177

Starting material	Product	MS *m/z* [M + 1]	Yield (g, %)[a]	Mp (°C)
1m	 **4m**	161.1	0.74, 93	148
1q	 **4q**	225.0	0.90, 80	163
1s	 **4s**	217.0	0.99, 92	182–183
2a	 **5a**	158.2	0.65, 82	159
2b	 **5b**	222.2/ 224.8	0.85, 76 (74.7, 67)[b]	130–153[c]
2c	 **5c**	170.2	0.81, 96	204
2d	 **5d**	215.0 [M – 1]	1.01, 93	187
2e	 **5e**	145.2	0.53, 73	227
2f	 **5f**	146.0	0.57, 79 (58.8, 81)[b]	183
2h	 **5h**	182.0	0.76, 84	107–123[c]
2i	 **5i**	183.2	0.69, 76	100–122[c]

[a] The isolated yield for pure compound obtained is given.
[b] The isolated yield for the scale-up to 0.5 mol of starting materials **1** and **2**.
[c] The specified substance decomposes during the measurement of melting point.

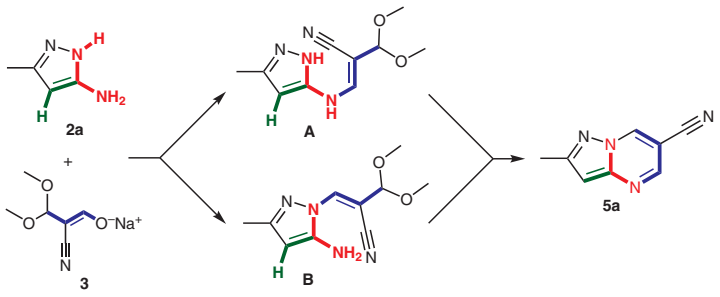
To further expand the elaborated procedure scope, we replaced the CCN binucleophiles into NCN. A representative set of NH-containing aminoheterocycles **2a–g** and amidines **2h**,**i** was examined in the reaction. Compound **2a** was a classical model substrate for investigating the place of primary attack by the electrophile, which we successfully used previously.[10b] The exclusive regioselective formation of pyrazolopyrimidine **5a** in high yield indicated that the reaction began from one of the nitrogen atoms followed by cyclization of the other. The possible pathway is shown in Scheme 3. The structure of **5a** was proved by NMR analysis. The characteristic proton bound to pyrazolic carbon is present as a singlet at δ = 6.7 ppm.

Other compounds also demonstrated excellent efficacy under the reaction conditions. All pyrimidines of type **5** were obtained in high preparative yields (73–96%), except **5g**, due to the low stability of the starting aminotetrazole **2g** under the reaction conditions. It should be noted that the reaction regioselectivity depends on the nucleophilic properties of the reaction centers. In the case of aminotriazole **2f**, where the reaction could involve two nitrogen atoms, only triazolopyrimidine **5f** formed. Such a reaction pathway could be explained by the higher nucleophilicity of the nitrogen atom in position 1 compared to nitrogen in position 4. The structure of **5f** has been proven by the X-ray crystal structure determination[16] (Figure 3).

The procedure was also explored for scale-up to multigram quantity (up to 100 g). The compounds **4a**,**h**,**k** and **5b**,**f** were obtained in 118–199 g quantity.

All data, including structures of the obtained compounds, parent ion peaks in mass spectra melting points and isolated yields, are summarized in Table 2.

In conclusion, the new, updated procedure for the reaction of aminoheterocycles and amidines with 3,3-dimethoxy-2-formylpropionitrile sodium salt leading to heteroannelated pyridines and/or pyrimidines was elaborated. Compared to the previously reported methods, the principal advantages were more mild conditions (r.t., lower quantity of HCl, optimized amount of the solvent). These changes allowed us to expand the scope and limitation of the reaction, to increase the yields, and to scale-up the process up to 100 g of products. It was shown that stability under the acidic reaction conditions and sufficient activity of nucleo-



Scheme 3 Possible pathway for regioselective formation of **5a**

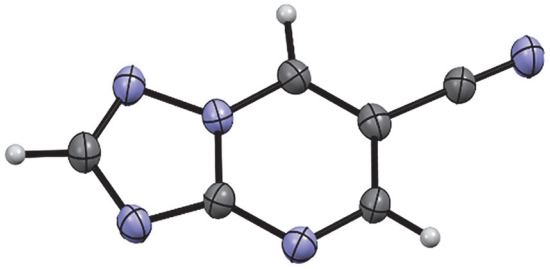


Figure 3 The X-ray molecular structure for compound **5f**

philic centers were the main criteria for the substrates for the efficient reaction. The sensitivity of the reaction products to the reagents nucleophilicity was rather high, allowing excellent regioselectivity. As a result, the advantages of the new methodology were demonstrated by the synthesis of 20 target heteroannelated pyridines/pyrimidines. Five new exclusive building blocks were obtained from readily available precursors with 67–91% yield in up to 100 g quantities.

The solvents were purified by the standard procedures. All starting materials were obtained from Enamine Ltd. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 126 or 101 MHz for ^{13}C). Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Their results were found to be in good agreement (±0.4%) with the calculated values. Mass spectra were measured on Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). The X-ray diffraction data sets were collected with a CMOS diffractometer. Programs used: data collection, APEX3 V2016.1-0;47 cell refinement and data reduction, SAINT V8.37A;48 absorption correction, SADABS V2014/7;49 structure solution; structure refinement, SHELXL-2015.[16]

The 3,3-dimethoxy-2-formylpropionitrile sodium salt **3** was prepared by the original procedure of Benoit.[12]

General Procedure for the Formation of 4 and 5 by the Cyclization of Aminoheterocycles 1 and 2 with 3,3-Dimethoxy-2-formylpropionitrile Sodium Salt 3

Salt **3** (6 mmol) was dissolved in MeOH (3 mL), then the concentrated aqueous solution of HCl (0.5 mL) and **1** or **2** (5 mmol) in MeOH (5 mL) were added. The reaction mixture was stirred for 4 h at r.t. After this, the additional MeOH (2 mL) and HCl (1.5 mL) were added. The reaction mixture was additionally stirred for 12 h at r.t. Then the saturated solution of $NaHCO_3$ was added dropwise to the reaction mixture until pH 7–8. After this, the target compound was extracted by $CHCl_3$ (3 × 30 mL). The organic layers were separated, combined, and dried over Na_2SO_4. The solvent was removed by evaporation under reduced pressure. The product was purified by preparative gradient chromatography on silica gel with 10% EtOAc in hexane. The compounds **4** or **5** were obtained as white powders. Yields, melting points, and LCMS data are given in Table 2. NMR data and R_f (for chromatographic purification using 10% EtOAc in hexane) are given below.

1-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4a)

R_f = 0.24.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.88 (dt, J = 15.5, 1.8 Hz, 2 H), 8.32 (d, J = 1.7 Hz, 1 H), 4.06 (d, J = 1.7 Hz, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 34.34, 101.65, 114.50, 118.46, 134.01, 136.95, 149.93, 151.13.

MS [M + 1]: m/z = 159.2.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 61.09; H, 3.89; N, 35.32.

1-(Propan-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4b)[17]

R_f = 0.21.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.83 (d, J = 12.5 Hz, 2 H), 8.48–8.12 (m, 1 H), 5.42–4.81 (m, 1 H), 1.46 (dd, J = 6.8, 3.1 Hz, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 21.62, 48.57, 101.29, 114.28, 117.90, 133.40, 136.39, 148.51, 150.26.

MS [M + 1]: m/z = 187.2.

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.5; H, 5.41; N, 30.09. Found: C, 64.65; H, 5.44; N, 29.98.

1,3-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4c)

R_f = 0.19.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.86–8.80 (m, 2 H), 3.99 (s, 3 H), 2.52 (d, J = 1.8 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 11.81, 33.34, 100.04, 113.57, 118.06, 135.78, 141.74, 150.51.

MS [M + 1]: *m/z* = 173.2.

Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.58; H, 4.92; N, 32.84.

1-*tert*-Butyl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4d)

R_f = 0.16.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.27 (s, 1 H), 2.01 (s, 3 H), 1.23 (s, 9 H).

^{13}C NMR (126 MHz, DMSO): δ = 11.95, 28.74, 28.93, 59.86, 99.97, 115.07, 118.12, 135.70, 140.34, 149.40, 149.86.

MS [M + 1]: *m/z* = 215.2.

Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 66,89; H, 6.26; N, 26.33.

3-Methyl-[1,2]oxazolo[5,4-*b*]pyridine-5-carbonitrile (4e)

R_f = 0.33.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (s, 2 H), 2.56 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 11.39, 106.09, 114.74, 117.77, 139.78, 154.97, 158.00, 170.32.

MS [M + 1]: *m/z* = 160.2.

Anal. Calcd for $C_8H_5N_3O$: C, 60.38; H, 3.17; N, 26.4. Found: C, 60.22; H, 3.32; N, 26.53.

3-(Propan-2-yl)-[1,2]oxazolo[5,4-*b*]pyridine-5-carbonitrile (4f)

R_f = 0.31.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.41–1.38 (m, 6 H), 9.19 (s, 1 H), 9.05 (s, 1 H), 3.41 (p, *J* = 6.8 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 20.26, 26.70, 105.09, 112.02, 116.61, 138.75, 153.77, 164.22, 169.44.

MS [M + 1]: *m/z* = 188.2.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.81; H, 4.87; N, 22.12.

1,3-Dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H*-pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4h)[18]

R_f = 0.19.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.11 (d, *J* = 2.1 Hz, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H), 3.55 (s, 3 H), 3.28 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 28.24, 29.48, 103.27, 109.51, 110.41, 110.46, 116.39, 140.77, 150.63, 152.38, 156.76, 159.56.

MS [M + 1]: *m/z* = 217.0.

Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.43; H, 3.85; N, 26.08.

Methyl 5-Cyanofuro[2,3-*b*]pyridine-2-carboxylate (4i)

R_f = 0.21.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.98 (s, 1 H), 8.87 (s, 1 H), 7.87 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 53.36, 106.44, 113.61, 117.44, 119.69, 138.58, 146.47, 151.37, 158.82, 162.48.

MS [M + 1]: *m/z* = 203.2.

Anal. Calcd for $C_{10}H_6N_2O_3$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.52; H, 3.22; N, 14.23.

Methyl 5-Cyanothieno[2,3-*b*]pyridine-2-carboxylate (4k)

R_f = 0.39.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.12 (s, 1 H), 9.00 (s, 1 H), 8.27 (s, 1 H), 3.93 (s, 3 H).

^{13}C NMR (126 MHz, DMSO): δ = 22.65, 53.68, 54.24, 99.97, 106.32, 117.50, 129.15, 131.77, 139.02, 151.31, 162.06.

MS [M + 1]: *m/z* = 219.0.

Anal. Calcd for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.77; N, 12.84; S, 14.69. Found: C, 55.38; H, 2.87; N, 13.13; S, 15.02.

Ethyl 5-Cyano-3-methylthieno[2,3-*b*]pyridine-2-carboxylate (4l)

R_f = 0.31.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.98 (s, 1 H), 8.88 (d, *J* = 9.1 Hz, 1 H), 4.37 (p, *J* = 6.2 Hz, 2 H), 2.68 (d, *J* = 6.5 Hz, 3 H), 1.36 (q, *J* = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO): δ = 12.66, 13.98, 61.76, 105.27, 117.05, 127.83, 132.43, 136.88, 139.03, 150.87, 151.05, 161.64, 162.72.

MS [M + 1]: *m/z* = 247.1.

Anal. Calcd for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.77; N, 12.84; S, 14.69. Found: C, 54.77; H, 2.61; N, 12.53; S, 14.37.

Thieno[3,2-*b*]pyridine-6-carbonitrile (4m)[12]

R_f = 0.49.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.07 (s, 1 H), 8.98 (s, 1 H), 8.47 (d, *J* = 5.3 Hz, 1 H), 7.68 (s, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 103.07, 117.64, 124.63, 131.87, 135.61, 138.08, 148.96, 157.48.

MS [M + 1]: *m/z* = 161.1.

Anal. Calcd for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49; S, 20.01. Found: C, 60.19; H, 2.47; N, 17.76; S, 19.66.

1-*tert*-Butyl-1*H*-pyrrolo[2,3-*b*]pyridine-3,5-dicarbonitrile (4q)

R_f = 0.24.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84–8.79 (m, 1 H), 8.73 (d, *J* = 3.2 Hz, 2 H), 1.75 (s, 9 H).

^{13}C NMR (101 MHz, DMSO): δ = 28.95, 59.87, 83.58, 102.92, 114.88, 118.26, 120.40, 133.02, 139.38, 146.80, 147.49.

MS [M + 1]: *m/z* = 225.0.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.68; H, 5.72; N, 25.11.

5,7-Dimethoxyquinoline-3-carbonitrile (4s)[19]

R_f = 0.42.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (d, *J* = 2.1 Hz, 1 H), 8.83 (d, *J* = 2.2 Hz, 1 H), 7.08 (d, *J* = 2.2 Hz, 1 H), 6.82 (d, *J* = 2.1 Hz, 1 H), 3.99 (s, 3 H), 3.96 (s, 3 H).

^{13}C NMR (101 MHz, DMSO): δ = 56.43, 56.91, 100.20, 100.60; 102.70, 118.31, 136.03, 136.29, 140.33, 151.52, 156.31, 164.50.

MS [M + 1]: *m/z* = 217.0.

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.9; H, 4.45; N, 13.04.

2-Methylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (5a)

R_f = 0.35.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.81 (d, *J* = 2.1 Hz, 1 H), 8.69 (t, *J* = 1.8 Hz, 1 H), 6.70 (s, 1 H), 2.45 (s, 3 H).

^{13}C NMR (126 MHz, DMSO): δ = 14.29, 93.42, 97.79, 97.79, 115.49, 141.61, 147.93, 148.98, 158.28.

MS [M + 1]: *m/z* = 158.2.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.95; H, 3.95; N, 35.82.

3-Bromopyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (5b)[20]

R_f = 0.46.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.01 (d, *J* = 2.0 Hz, 1 H), 8.85 (d, *J* = 2.0 Hz, 1 H), 8.60 (s, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 85.68, 95.56, 114.91, 143.31, 144.13, 147.84, 150.45.

MS [M + 1]: *m/z* = 222.2/224.8.

Anal. Calcd for $C_7H_3BrN_4$: C, 37.7; H, 1.36; N, 25.12; Br, 35.83. Found: C, 37.62; H, 1.48; N, 24.81; Br, 36.1.

Pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitrile (5c)

R_f = 0.48.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.22 (s, 1 H), 9.14 (s, 1 H), 8.99 (s, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 83.15, 97.88, 112.33, 114.36, 144.23, 149.59, 150.04, 153.79.

MS [M + 1]: *m/z* = 170.2.

Anal. Calcd for $C_8H_3N_5$: C, 56.81; H, 1.79; N, 41.4. Found: C, 56.44; H, 2.09; N, 41.55.

Ethyl 6-Cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (5d)

R_f = 0.42.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.15 (d, *J* = 2.2 Hz, 1 H), 8.82 (d, *J* = 2.2 Hz, 1 H), 8.69 (s, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO): δ = 14.78, 60.51, 97.26, 104.03, 115.20, 144.12, 146.98, 150.20, 153.36, 161.57.

MS [M – 1]: *m/z* = 215.0 NEG.

Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.77; H, 3.61; N, 25.59.

Imidazo[1,2-*a*]pyrimidine-6-carbonitrile (5e)

R_f = 0.42.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.81 (d, *J* = 2.4 Hz, 1 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.06 (s, 1 H), 7.90 (s, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 94.95, 113.50, 115.47, 136.48, 142.33, 146.41, 149.43.

MS [M + 1]: *m/z* = 145.2.

Anal. Calcd for $C_7H_4N_4$: C, 58.33; H, 2.8; N, 38.87. Found: C, 58.03; H, 2.49; N, 38.6.

[1,2,4]Triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5f)

R_f = 0.38.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.28 (q, *J* = 2.7, 2.1 Hz, 1 H), 9.21 (q, *J* = 2.7, 2.2 Hz, 1 H), 8.91–8.84 (m, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 97.57, 114.53, 143.87, 154.53, 155.93, 158.01.

MS [M + 1]: *m/z* = 146.0.

Anal. Calcd for $C_6H_3N_5$: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.58; H, 1.92; N, 48.51.

2-Phenylpyrimidine-5-carbonitrile (5h)[21]

R_f = 0.43.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.31 (d, *J* = 2.6 Hz, 1 H), 8.43–8.35 (m, 2 H), 7.56 (dt, *J* = 15.1, 7.2 Hz, 3H).

^{13}C NMR (126 MHz, DMSO): δ = 107.24, 116.03, 129.07, 129.51, 132.91, 136.07, 161.28, 165.09.

MS [M + 1]: *m/z* = 182.0.

Anal. Calcd for $C_{11}H_7N_3$: C, 72.92; H, 3.89; N, 23.19. Found: C, 73.22; H, 3.68; N, 23.35.

2-(Pyridin-3-yl)pyrimidine-5-carbonitrile (5i)

R_f = 0.36.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.49 (d, *J* = 2.3 Hz, 1 H), 9.46 (s, 1 H), 9.40 (s, 1 H), 8.77 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.66 (dt, *J* = 8.0, 2.1 Hz, 1 H), 7.59 (dd, *J* = 8.0, 4.8 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO): δ = 107.41, 115.31, 124.03, 131.20, 135.85, 149.55, 152.67, 160.96, 163.27.

MS [M + 1]: *m/z* = 183.2.

Anal. Calcd for $C_{10}H_6N_4$: C, 65.93; H, 3.32; N, 30.75. Found: C, 66.05; H, 3.29; N, 30.56.

General Procedure for Scale-Up of Heterocyclization

Salt **3** (0.55 mol) was dissolved in MeOH (350 mL), then concentrated aqueous solution of HCl (50 mL) and **1a**,**h**,**k** or **2b**,**f** (0.5 mol) in MeOH (550 mL) were added. The reaction mixture was stirred for 4 h at r.t. After this, an additional MeOH (2 mL) and HCl (1.5 mL) were added. The reaction mixture was additionally stirred for 12 h at r.t. Then, the saturated solution of $NaHCO_3$ was added dropwise to the reaction mixture for pH = 7–8. After this, the target compound was extracted by $CHCl_3$ (5 × 500 mL). The organic layer was separated, combined, and dried over Na_2SO_4. The solvent was removed by evaporation under reduced pressure. The pure product was separated by flash gradient chromatography on silica gel with hexanes–EtOAc (1:0 to 1:1). The compounds **4a**,**h**,**k** or **5b**,**f** were obtained as white powders. Yields are given in Table 2.

Funding Information

The work was funded by Enamine Ltd. and supported by the Ministry of Education and Science of Ukraine (Grant Number 0120U102179).

Acknowledgment

The authors thank Prof. Andrey Tolmachev for his encouragement and support and Mr. Dmytro Yehorov for his help in manuscript preparation.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1360-9852.

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