Directed Solid-Phase Synthesis of Trisubstituted Imidazo[4,5-c]pyridines and Imidazo[4,5-b]pyridines

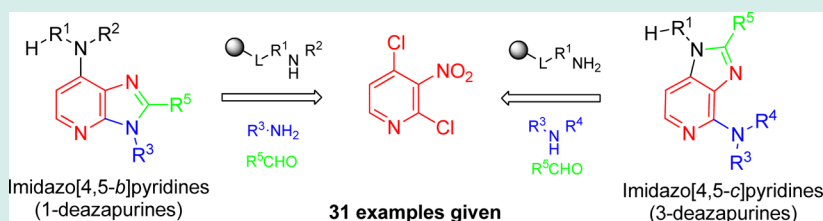Barbora Lemrová,[†] Petra Smyslová,[†] Igor Popa,[†] Tomáš Oždian,[‡] Pawel Zajdel,[§] and Miroslav Soural*,[†]

[†]Department of Organic Chemistry, Institute of Molecular and Translational Medicine, Faculty of Science, Palacký University, 17. Listopadu 12, 771 46 Olomouc, Czech Republic

[‡]Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University and University Hospital in Olomouc, Hněvotínská 5, 775 15 Olomouc, Czech Republic

[§]Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland

Ⓢ *Supporting Information*

Imidazo[4,5-b]pyridines
(1-deazapurines)

31 examples given

Imidazo[4,5-c]pyridines
(3-deazapurines)

ABSTRACT: An efficient method is described for the solid-supported synthesis of imidazo[4,5-b]pyridines and imidazo[4,5-c]pyridines from 2,4-dichloro-3-nitropyridine. The key pyridine building block was reacted with polymer-supported amines, followed by replacement of the second chlorine with amines, nitro group reduction, and imidazole ring closure with aldehydes. Depending on the combination of polymer-supported and solution-phase reagents, the strategy allowed for the simple preparation of the target trisubstituted derivatives with variable positioning of the pyridine nitrogen atom. Additionally, after a slight modification of the method, the preparation of strictly isomeric imidazopyridines was possible.

KEYWORDS: solid-phase synthesis, imidazo[4,5-b]pyridines, imidazo[4,5-c]pyridines, 1-deazapurines, 3-deazapurines, 2,4-dichloronitropyridine

■ INTRODUCTION

Compounds based on the imidazopyridine scaffold represent a large group of condensed nitrogenous heterocycles. Depending on the mutual location of the pyridine and imidazole scaffold and the resulting tautomery, different classes of imidazopyridines have been described (Figure 1).

Within the entire group of imidazopyridine derivatives, 1H-imidazo[4,5-c]pyridines (referred to as 3-deaza-9H-purines) and 1H-imidazo[4,5-b]pyridines (referred to as 1-deaza-9H-purines) represent the privileged structures in medicinal chemistry due to their isostericity with the 9H-purine scaffold. Both groups of compounds have been intensively studied, and various pharmacological properties have been observed. For instance, derivatives of imidazo[4,5-c]pyridines were identified as potent anti-HCV agents,[1] A2A adenosine receptor antagonists,[2] and protein kinase B inhibitors;[3] also inhibition of AKT kinase[4] and fungicidal,[5] antitumor,[6] and anti-hypertensive[7] activities were observed. Similarly, imidazo[4,5-b]pyridines exhibit a wide range of biological properties, such as anticancer,[6] antimalarial,[8] antifungal,[9] antiviral,[10] anticonvulsant, and anxiolytic effects[11] (Figure 2).

Decoration of the deazapurine scaffold with different substituents and variation of the nitrogen atom positions strongly influence the resulting biological properties.[12,13] A typical example is sulmazole, an imidazo[4,5-b]pyridine-based cardiotonic agent. Sulmazole exhibits a high ionotropic effect, whereas its isomeric imidazo[4,5-c]pyridine analogue isomazole is inactive (Figure 3).[14]

Considering this dependence on the nitrogen atom location, we developed a high-throughput synthetic strategy that prepares either 1-deazapurines or 3-deazapurines bearing diverse substituents in different positions. With respect to the large number of available building blocks (various primary and secondary amines and aldehydes), we focused on the application of polymer-supported chemistry. This technique has been reported to be powerful tool for the simple preparation of chemical libraries using the combinatorial chemistry concept.[15,16] The elaborated approach (Scheme 1) was inspired by the previously reported routes of solid-phase synthesis for purines starting from immobilized amines and dihalogenpyrimidines.[17−20] In the present study, although the same key building block (2,4-dichloro-3-nitropyridine) is used for routes A and B, different amino compounds (primary or secondary) added via different methods (polymer-supported or
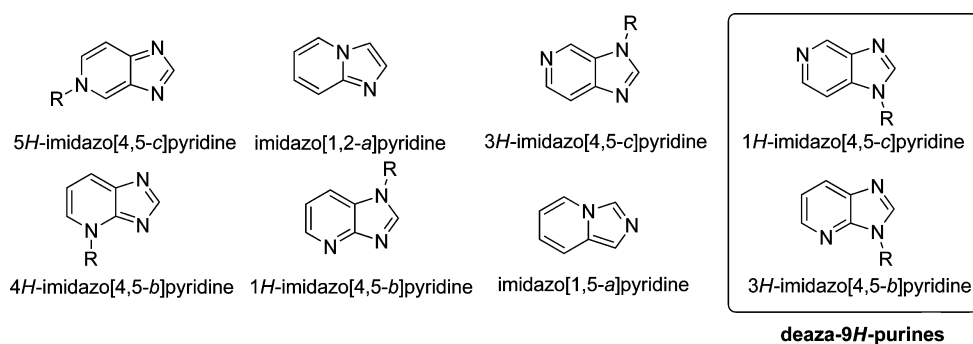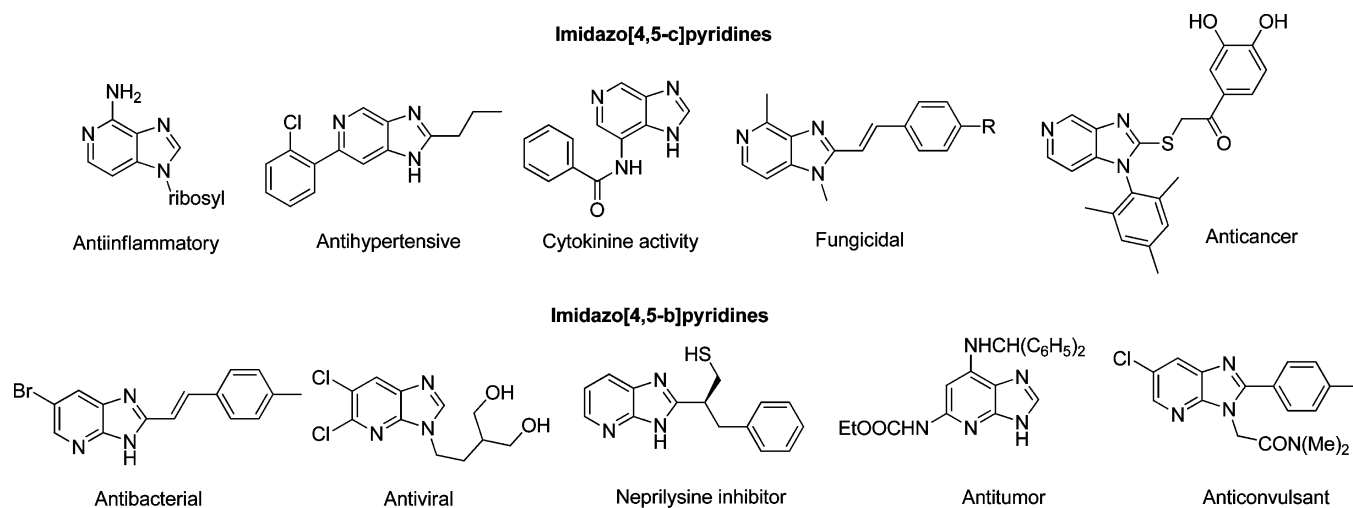
Figure 1. Family of imidazopyridines.

Figure 2. Selected representatives of biologically active compounds bearing the target imidazopyridine scaffold.
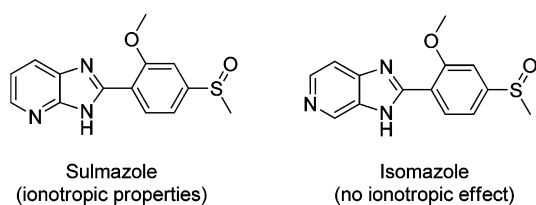

Figure 3. Example of the structure–activity dependence based on the location of the pyridine nitrogen atom.

solution-phase) direct the positioning of the pyridine nitrogen atom, thus yielding different deazapurines.

■ RESULTS AND DISCUSSION

Various starting amino compounds (Scheme 2) were immobilized using three common polystyrene-based resins with suitable acid-labile linkers: Wang resin,[21] Rink amide resin,[22] and aminomethyl resin equipped with a BAL linker (4-(4-formyl-3-methoxyphenoxy)butanoic acid).[23] Wang resin was

Scheme 1. Retrosynthetic Suggested Strategy for the Preparation of the Target Imidazo[4,5-b]pyridines and Imidazo[4,5-c]pyridines
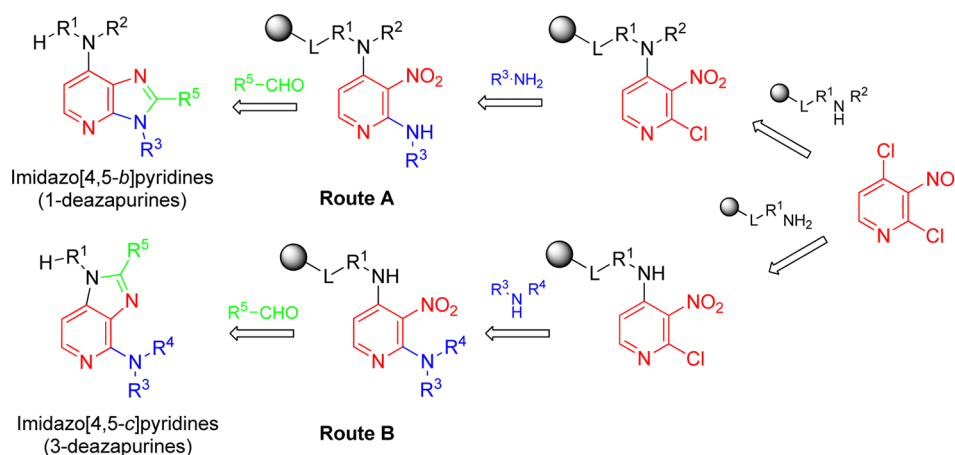
Scheme 2. Strategies and Methods for the Preparation of Immobilized Amines[a]
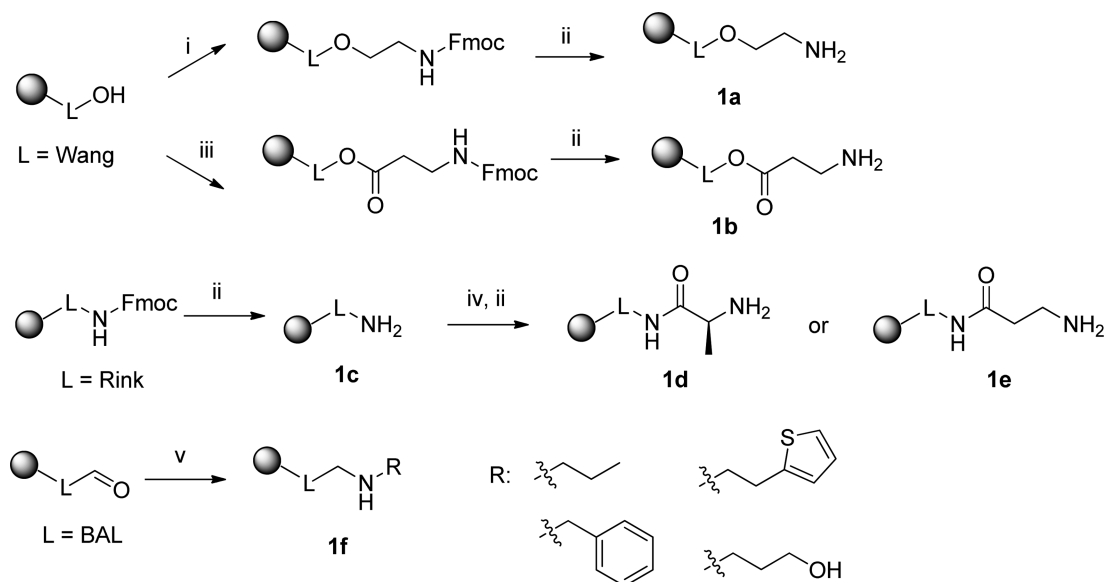
[a]Reagents and conditions: (i) trichloroacetonitrile, DBU, DCM, 2 h, rt, then 2-(Fmoc-amino)ethanol, BF$_3$·Et$_2$O, THF 1 h, rt; (ii) 20% piperidine in DMF, 20 min, rt; (iii) Fmoc-amino acid, HOBt, DIC, DMAP, DMF, DCM, rt, overnight; (iv) Fmoc-amino acid, HOBt, DIC, DMF, DCM, rt, overnight; (v) amine, 10% AcOH/DMF, rt, overnight, then NaBH(OAc)$_3$, 4 h, rt.

Scheme 3. Solid-Phase Synthesis of 3-Deazapurine Derivatives[a]
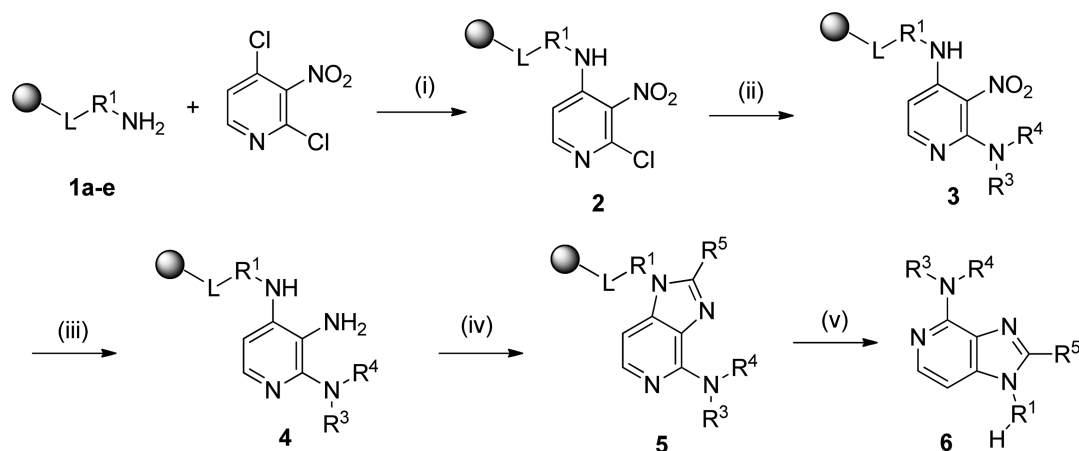
[a]Reagents and conditions: (i) 2,4-dichloro-3-nitropyridine, EDIPA, DMSO, rt, overnight; (ii) 10% secondary amine in DMSO, rt, overnight; (iii) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, DCM/H$_2$O, rt, overnight; (iv) aldehyde, DMSO, 80 °C, overnight; (v) 50% TFA in DCM, rt, 1 h. For identification of R$^{1,3-5}$, see Table 1.
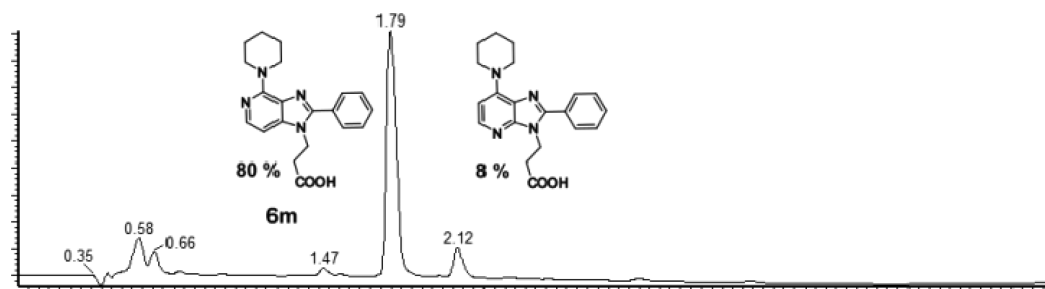
Figure 4. HPLC-UV chromatogram of the crude mixture of **6m** (t_R = 1.79 min) and its isomeric side product (t_R = 2.12 min).

used to attach either suitably protected amino alcohols (such as 2-(Fmoc-amino)ethanol, resin **1a**) via an ether bond,[24] leading to final compounds with terminal hydroxy groups, or Fmoc-amino acids (such as Fmoc-β-Ala-OH, resin **1b**) via an ester bond, leading to final compounds with a terminal carboxylic group. The latter alternative was not applicable for α-amino acids due to an intramolecular aminolysis of ester bond leading to release of quinoxalinone derivative by cyclative cleavage

Table 1. List of the Prepared Imidazo[4,5-*c*]pyridines (3-Deazapurines) from Scheme 3

compd	starting resin/R^1	amine to give R^{3}R^4	R^5	purity^a (%)/yield^b (%)
6a	1e/(CH$_2$)$_2$CONH$_2$	piperidine	C$_6$H$_5$	73/48
6b	1e/(CH$_2$)$_2$CONH$_2$	morpholine	C$_6$H$_5$	64/59
6c	1e/(CH$_2$)$_2$CONH$_2$	dipropylamine	C$_6$H$_5$	61/45
6d	1e/(CH$_2$)$_2$CONH$_2$	pyrrolidine	C$_6$H$_5$	40/20
6e	1e/(CH$_2$)$_2$CONH$_2$	diethanolamine	C$_6$H$_5$	66/50
6f	1e/(CH$_2$)$_2$CONH$_2$	piperidine	4-(CH$_3$O)C$_6$H$_5$	64/31
6g	1e/(CH$_2$)$_2$CONH$_2$	piperidine	furan-2-yl	70/50
6h	1e/(CH$_2$)$_2$CONH$_2$	piperidine	4-(NO$_2$)C$_6$H$_5$	67/56
6i	1e/(CH$_2$)$_2$CONH$_2$	piperidine	CH$_3$	61/30
6j	1d/(CH)CH$_3$CONH$_2$	piperidine	C$_6$H$_5$	49/39
6k	1c/−	piperidine	C$_6$H$_5$	66/57
6l	1a/(CH$_2$)$_2$OH	piperidine	C$_6$H$_5$	60/53
6m	1b/(CH$_2$)$_2$COOH	piperidine	C$_6$H$_5$	80/71
6n	1b/(CH$_2$)$_2$COOH	morpholine	4-(NO$_2$)C$_6$H$_5$	70/68

^{a}Crude purity after the reaction sequence according to integrated HPLC-UV chromatograms. ^{b}Overall yield after all reaction steps and HPLC purification.

Scheme 4. Solid-Phase Synthesis of 1-Deazapurine Derivatives^a
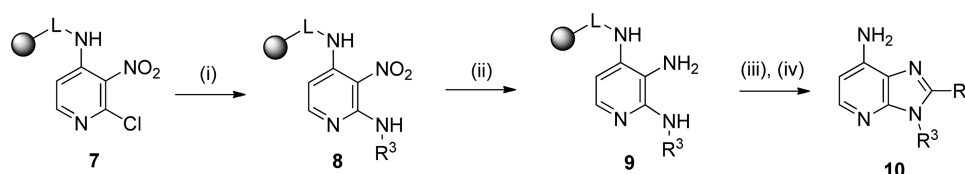
^{a}Reagents and conditions: (i) primary amine, DMSO, rt, overnight; (ii) Na$_2$S$_2$O$_4$, K$_2$CO$_3$, TBAHS, DCM/H$_2$O, rt, overnight; (iii) aldehyde, DMSO, 80 °C, overnight; (iv) 50% TFA in DCM, rt, 1 h. For identification of R^{3,5}, see Table 2.

**Table 2. List of the Prepared Imidazo[4,5-*b*]pyridines 10 from Scheme 4**

compd	starting resin	R^3	R^5	purity^a (%)/yield^b (%)
10a	1c	pentyl	C$_6$H$_5$	77/71
10b	1c	N-(2-(piperidin-1-yl)ethyl)	C$_6$H$_5$	72/60
10c	1c	hydroxypropyl	C$_6$H$_5$	61/39
10d	1c	cyclopentyl	C$_6$H$_5$	52/55
10e	1c	2-(thiophen-2-yl)ethyl	C$_6$H$_5$	60/51
10f	1c	pentyl	CH$_3$	65/28
10g	1c	pentyl	4-(MeO)C$_6$H$_5$	66/33
10h	1c	pentyl	furan-2-yl	60/30
10i	1c	pentyl	4-(NO$_2$)C$_6$H$_5$	78/46

^{a}Crude purity after the reaction sequence according to integrated HPLC-UV chromatograms. ^{b}Overall yields after all reaction steps and HPLC purification.

(Scheme 3, intermediates 4, R^1 = −OCOCH(CH$_3$)−).[25] In contrast, a Rink amide resin, resulting in a more stable connection via an amide bond, was successfully used for α-amino acids; this was tested with Fmoc-Ala-OH (resin 1d, final product 6j). A similar attachment was also tested for β-amino acids (Fmoc-β-Ala-OH, resin 1e). Further, the Rink amide resin 1c was directly used for arylation with 2,4-dichloro-3-nitro-pyridine. To obtain resin-bound secondary amines, an amino-methyl polystyrene-based resin equipped with a BAL linker was used to immobilize various primary amines by reductive amination (resin 1f).

Preparation of Imidazo[4,5-c]pyridines (3-Deazapurines). The synthetic pathway for 3-deazapurine isomers is depicted in Scheme 3. To test the applicability of this general method for preparation of the imidazo[4,5-*c*]pyridine scaffold, resin 1b was used.

Resin 1b was arylated with a 0.5 M solution of 2,4-dichloro-3-nitropyridine in the presence of N-ethyldiisopropylamine (EDIPA) in dimethyl sulfoxide (DMSO). The reaction was not completely regioselective, and two isomers were detected in an approximately 8.5 (substitution in position 4)-to-1.5 (substitution in position 2) ratio, calculated from LC-UV chromatograms. The same results were observed for polymer-supported primary amines 1a, 1c, 1d, and 1e and resin-bound secondary amines (resin 1f). Subsequently, the chlorine atom of intermediate 2 was substituted with piperidine. The reaction was conducted using a 10% solution of a secondary amine in DMSO overnight at room temperature. In the next step, the nitro group was reduced by sodium dithionate in the presence of potassium carbonate and tetrabutylammonium hydrogen-sulfate, as described previously.[26] The last step on solid support was the cyclization reaction of intermediate 4 with aldehyde. Benzaldehyde was used as the model building block. Under

Scheme 5. Strategy for the Preparation of Strictly Isomeric Imidazo[4,5-b]pyridines and Imidazo[4,5-c]pyridines[a]
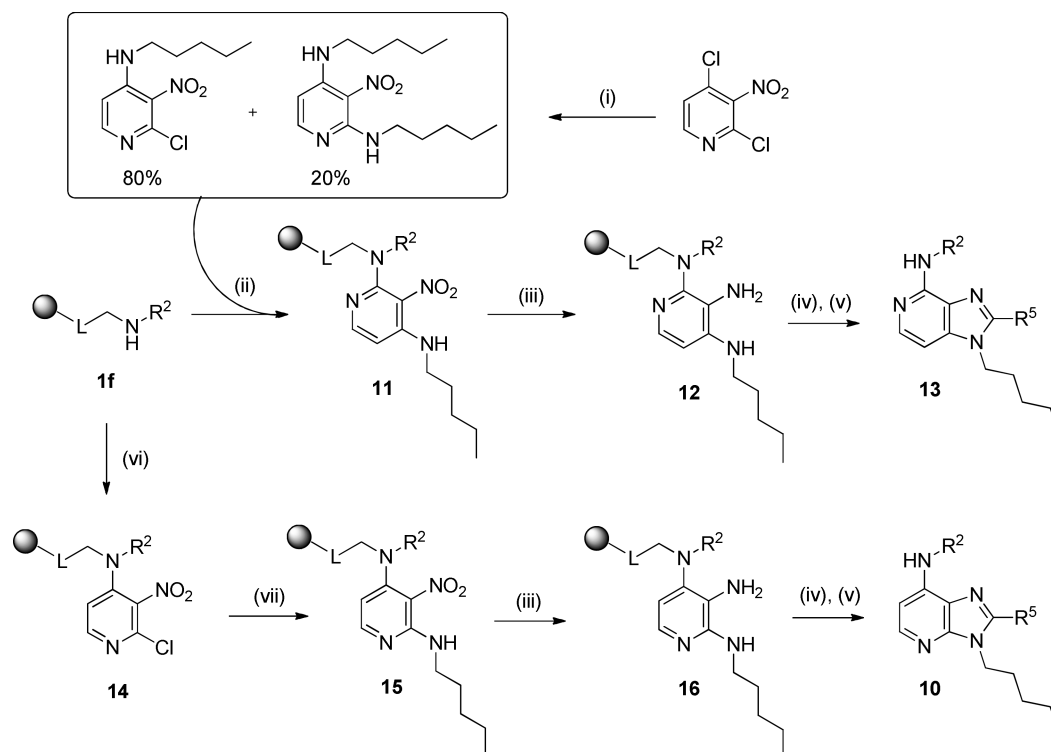
[a]Reagents and conditions: (i) n-pentylamine, EDIPA, DMSO, rt, overnight; (ii) EDIPA, 70 °C, overnight; (iii) $Na_2S_2O_4$, K_2CO_3, TBAHS, DCM/H_2O, rt, overnight; (iv) aldehyde, DMSO, 80 °C, overnight; (v) 50% TFA in DCM, rt, 1 h.; (vi) 2,4-dichloro-3-nitropyridine, EDIPA, DMSO, rt, overnight; (vii) n-pentylamine, DMSO, 80 °C, overnight. For identification of $R^{2,5}$, see Table 3.

Table 3. List of Isomeric 1- and 3-Deazapurines from Scheme 5

compd	starting resin	R^2	R^5	purity[a] (%)/ yield[b] (%)
10j	1f	$-(CH_2)_3OH$	C_6H_5	66/36
13a	1f	$-(CH_2)_3OH$	C_6H_5	74/65
10k	1f	$-(CH_2)_2CH_3$	C_6H_5	80/51
13b	1f	$-(CH_2)_2CH_3$	C_6H_5	66/12
10l	1f	$-(CH_2)C_6H_5$	C_6H_5	75/64
13c	1f	$-(CH_2)C_6H_5$	C_6H_5	63/61
10m	1f	2-(thiophen-2-yl)ethyl	C_6H_5	80/32
13d	1f	2-(thiophen-2-yl)ethyl	C_6H_5	68/26

[a]Crude purity after the reaction sequence according to integrated HPLC-UV chromatograms. [b]Overall yield after all reaction steps and HPLC purification.

mild conditions (0.2 M benzaldehyde in dichloromethane (DCM) or N,N-dimethylformamide (DMF) at room temperature), the reaction was not completed, and unreacted starting material was observed. In addition, the target product was accompanied by a compound with a molecular weight 2 units higher. This molecular weight corresponds to either dihydro-3-deazapurine[27] or the corresponding Schiff's base intermediate. To obtain the imidazopyridine product, we tested different temperatures, aldehyde concentrations, and solvents. Complete conversion and 80% crude purity (LC-UV spectra) of the product **6m** were observed after the reaction with 0.5 M benzaldehyde in DMSO at 80 °C for 16 h. The LC-UV-MS data of the crude product **6m** indicated the presence of the alternative imidazopyridine isomer formed by non-regio-selective arylation with 2,4-dichloro-3-nitropyridine (caused by minor nucleophilic substitution in position 4 instead of position 2, see Figure 4). Both compounds were isolated with semipreparative reverse-phase HPLC and fully characterized, although the side product was obtained in very low yield. The overall yield of **6m** after purification was 71%.

To evaluate the limitation and scope of the synthetic route for the preparation of diverse imidazo[4,5-c]pyridines, we subsequently tested different polymer-supported primary amines (resins **1a**, **1b**, **1c**, and **1d**), various secondary amines
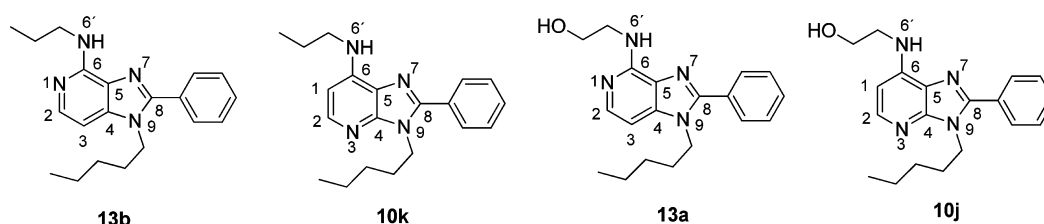

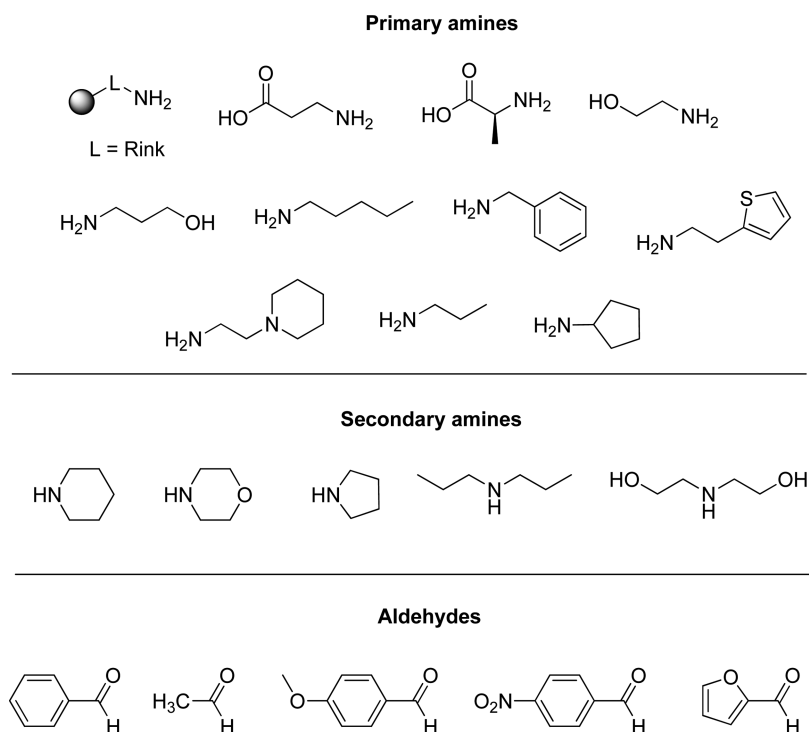**Figure 5.** Compounds used to confirm the resulting isomers.

Figure 6. Complete list of building blocks successfully used for the preparation of the target imidazopyridines.

(morpholine, pyrrolidine, diethanolamine, and dipropylamine) and aldehydes (furfural, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, and acetaldehyde). All products (**6a**−**6n**) were prepared with good crude purity and overall yield (Table 1).

Preparation of Imidazo[4,5-*b*]pyridines (1-Deazapurines). A similar strategy was used for the preparation of 1-deazapurine derivatives (Scheme 4). The synthetic pathway was initially tested with the Rink amide resin **1c**. Preparation of the target compound **10** followed the procedures described for imidazo[4,5-*c*]pyridines; however, substitution of the chlorine atom of intermediate **7** was performed using a primary, instead of secondary, amine (Scheme 4, step (i)).

Although the intermediate obtained after the reduction of **8** may undergo two possible cyclization routes, leading to either imidazo[4,5-*c*]pyridine or imidazo[4,5-*b*]pyridine scaffold, only the formation of the latter was observed. Similar reactivity was described by Hammarström for solid-phase purine chemistry.[20] However, cyclization of intermediate **4**, leading to compound **6k** (Scheme 3, Table 1), proceeded toward imidazo[4,5-*c*]-pyridine when it was not possible to cyclize into imidazo-[4,5-*b*]pyridine. Such ring-closure regioselectivity provides an efficient tool for the directed preparation of 1-deazaadenine derivatives (Table 2) or N^9-unsubstituted 3-deazapurine derivatives (Table 1, **6k**) based on the selection of primary or secondary amines to substitution for the pyridine chlorine atom at position 2. The alternative approach, leading to imidazo[4,5-*b*]pyridines, was successfully tested using resin **1c** with various combinations of building blocks, including different primary amines (pentylamine, 2-(thiophen-2-yl)-ethanamine, 2-(piperidin-1-yl)ethanamine, 3-aminopropanol, and cyclopentylamine) and aldehydes (furfural, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, and acetaldehyde).

To generate additional variation in the amino group at position C^7, the Rink amide resin was replaced with the polymer-supported secondary amine **1f** (Scheme 5). In this manner, four additional imidazo[4,5-*c*]pyridines (**10j**−**10m**) were synthesized using the strategy described in the next section.

Preparation of Strictly Isomeric Imidazo[4,5-*b*]-pyridines and Imidazo[4,5-*c*]pyridines. Although the above-mentioned solid-phase strategies enable the simple synthesis of a large number of corresponding deazapurines, this method is not capable of producing fully isomeric imidazopyridines, i.e., compounds containing the same ligands in specific positions and differing only in the location of the pyridine nitrogen atom. To overcome this drawback, we developed an efficient synthetic pathway based on the combination of solution-phase and solid-phase syntheses (Scheme 5). Imidazo[4,5-*b*]pyridines **10j**−**10m** (Table 3) were prepared using the strategy introduced earlier from polymer-supported secondary amines (resin **1f**). After arylation with 2,4-dichloro-3-nitropyridine, *n*-pentylamine was used as the model primary amine for substitution of the chlorine atom of intermediate **14**, which directed the cyclization toward the 1-deazapurine scaffold. To synthesize the opposite isomers, solution-phase pre-modification of the key building block was necessary (Scheme 5).

Thus, 2,4-dichloro-3-nitropyridine was reacted with 2 equiv of *n*-pentylamine and EDIPA in DMSO to give a mixture of the desired monosubstituted product and a disubstituted pyridine derivative (ratio of 8:2, according to HPLC-UV chromatograms). Without any purification or workup, the reaction mixture was immediately treated with resin **1f** and another 1 equiv of EDIPA and was shaken at 70 °C for 16 h. After the resin was washed, pure intermediate **11** was obtained, which was transformed to the final product **13** using the developed procedures. Ultimately, four pairs of corresponding isomers were synthesized with good crude purity and yield (Table 3).

The isomeric identities of all reported compounds were based on the presumption that the nucleophilic substitution of

2,4-dichloro-3-nitropyridine is preferentially targeted to the C^4 position. This course of reaction was previously described;[28,29] however, unambiguous evidence for this has yet to be reported. Therefore, we submitted two pairs of structural isomers (**13b**, **10k**, **13a**, and **10j**, Figure 5) to a thorough NMR study. A detailed assignment of individual atoms using 2D $^1H-^1H$ gCOSY, $^1H-^{13}C$ gHMQC, and $^1H-^{13}C$ gHMBC was completed (see Supporting Information).

Subsequently, 2D $^1H-^{15}N$ gHMBC was used to confirm the suggested structural assignment. In the case of **13b**, the position of N^1 (δ = 235.81 ppm) was confirmed by the presence of a high-intensity cross peak to HC^2 (7.75 ppm, d, 13.8 Hz), a low-intensity cross peak to HC^3 (6.76 ppm, s), and a high-intensity cross peak to $HN^{6'}$ (6.63 ppm, s). In contrast, the isomeric derivative **10k** exhibited a single cross peak to HC^1 (6.44, s), which confirms the presence of the N^3 atom (δ = 234.94 ppm). Similar results were obtained for the analogous isomers **13a** and **10j**. In the first case, the N^1 position (δ = 192.03 ppm) was established by the presence of a high-intensity cross peak to HC^2 (7.72 ppm, s) and a low-intensity cross peak to HC^3 (7.02 ppm, s). The N^3 position of the structural isomer **10j** (δ = 230.69 ppm) gave a high-intensity cross peak to HC^2 (7.89 ppm, d, 13.6 Hz) and a low-intensity cross peak to HC^1 (6.33 ppm, s).

In conclusion, we have developed an efficient method for the solid-phase synthesis of trisubstituted 1- and 3-deazapurines from the key building block, 2,4-dichloro-3-nitropyridine. Considering the large number of commercially available starting materials (primary and secondary amines and aldehydes), the method can be used for the simple preparation of sizable chemical libraries of diversely substituted imidazopyridines. The versatility of the method was highlighted using a variety of starting materials (Figure 6) and demonstrated by the preparation and full characterization of 31 model compounds. Additionally, a simple method for preparing strictly isomeric 1- and 3-deazapurines was developed to allow detailed structure–activity relationship studies of imidazopyridines to specifically target the position of the pyridine nitrogen atom.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of experimental synthetic and analytical procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: soural@orgchem.upol.cz.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Gupta, S. P.; Samanta, S.; Masand, N.; Patil, V. M. *k* nearest neighbor-molecular field analysis on human HCV NS5B polymerase inhibitors: 2,5-disubstituted imidazo[4,5-c]pyridines. *Med. Chem. Res.* **2013**, *22*, 330–339.

(2) Minetti, P.; Tinti, M. O.; Carminati, P.; Castorina, M.; Di Cesare, M. A.; Di Serio, S.; Gallo, G.; Ghirardi, O.; Giorgi, F.; Giorgi, L.; Piersanti, G.; Bartoccini, F.; Tarzia, G. 2- n-Butyl-9-methyl-8-[1,2,3]triazol-2-yl-9H-purin-6-ylamine and Analogues as A2A Adenosine Receptor Antagonists. Design, Synthesis, and Pharmacological Characterization. *J. Med. Chem.* **2005**, *48* (22), 6887–6896.

(3) Heerding, D. A.; Rouse, M. B.; Seefeld, M. A. Inhibitors of Akt activity. PCT WO2006113837.

(4) Rouse, M. B.; Seefeld, M. A.; Leber, J. D.; McNulty, K. C.; Sun, L.; Miller, W. H.; Zhang, S. Y.; Minthorn, E. A.; Concha, N. O.; Choudhry, A. E.; Schaber, M. D.; Heerding, D. A. Aminofuratans as potent inhibitors of AKT kinase. *Bioorg. Med. Chem. Lett.* **2009**, *19* (5), 1508–1511.

(5) Yutilov, Yu. M.; Ignatenko, A. G.; Andreeva, E. I.; Bobkova, G. V.; Mikhailova, L. E. Synthesis and fungicidal activity of styryl derivatives of imidazo[4,5-c]pyridine. *Fiziol. Akt. Veshchestva* **1989**, *21*, 77–80.

(6) Hranjec, M.; Lučić, B.; Ratkaj, I.; Pavelić, S. K.; Piantanida, I.; Pavelić, K.; Karminski-Zamola, G. Novel imidazo[4,5-b]pyridine and triaza-benzo[c]fluorene derivatives: Synthesis, antiproliferative activity and DNA binding studies. *Eur. J. Med. Chem.* **2011**, *46* (7), 2748–2758.

(7) Stavenger, R. A.; Cui, H.; Dowdell, S. E.; Franz, R. G.; Gaitanopoulos, D. E.; Goodman, K. B.; Hilfiker, M. A.; Ivy, R. L.; Leber, J. D.; Marino, J. P., Jr.; Oh, H.-J.; Viet, A. Q.; Xu, W.; Ye, G.; Zhang, D.; Zhao, Y.; Jolivette, L. J.; Head, M. S.; Semus, S. F.; Elkins, P. A.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Doe, Ch. P.; Bentley, R.; Chen, Z. X.; Hu, E.; Lee, D. Discovery of Aminofurazan-azabenzimidazoles as Inhibitors of Rho-Kinase with High Kinase Selectivity and Antihypertensive Activity. *J. Med. Chem.* **2007**, *50* (1), 2–5.

(8) Hameed P, S.; Chinnapattu, M.; Shanbag, G.; Manjrekar, P.; Koushik, K.; Raichurkar, A.; Patil, V.; Jatheendranath, S.; Rudrapatna, S. S.; Barde, S. P.; Rautela, N.; Awasthy, D.; Morayya, S.; Narayan, Ch.; Kavanagh, S.; Saralaya, R.; Bharath, S.; Viswanath, P.; Mukherjee, K.; Bandodkar, B.; Srivastava, A.; Panduga, V.; Reddy, J.; Prabhakar, K. R.; Sinha, A.; Jimenez-Diaz, M. B.; Martinez, M. S.; Angulo-Barturen, I.; Ferrer, S.; Sanz, L. M.; Gamo, F. J.; Duffy, S.; Avery, V. M.; Magistrado, P. A.; Lukens, A. K.; Wirth, D. F.; Waterson, D.; Balasubramanian, V.; Iyer, P. S.; Narayanan, S.; Hosagrahara, V.; Sambandamurthy, V. K.; Ramachandran, S. Aminoazabenzimidazoles, a Novel Class of Orally Active Antimalarial Agents. *J. Med. Chem.* **2014**, *57* (13), 5702–5713.

(9) Lavanya, P.; Suresh, M.; Kotaiah, Y.; Harikrishna, N.; Venkata Rao, C. Synthesis, antibacterial, antifungal and antioxidant activity studies on 6-Bromo-2-substitutedphenyl-1H-imidazo[4,5-b]pyridine. *Asian J. Pharm. Clin. Res.* **2011**, *4* (4), 69–73.

(10) Li, X.; Zhan, P.; Liu, H.; Li, D.; Wang, L.; Chen, X.; Liu, H.; Pannecouque, Ch.; Balzarini, J.; De Clercq, E.; Liu. Arylazolyl(azinyl)thioacetanilides. Part 10: Design, synthesis and biological evaluation of novel substituted imidazopyridinylthioacetanilides as potent HIV-1 inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *20* (18), 5527–5536.

(11) Tomczuk, B. E.; Taylor, C. R., Jr; Moses, L. M.; Sutherland, D. B.; Lo, Y. S.; Johnson, D. N.; Kinnier, W. B.; Kilpatrick, B. F. 2-Phenyl-3H-imidazo[4,5-b]pyridine-3-acetamides as non-benzodiazepine anticonvulsants and anxiolytics. *J. Med. Chem.* **1991**, *34* (10), 2993–3006.

(12) Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. S. Structure-activity relationships of arylimidazopyridine cardiotonics: discovery and inotropic activity of 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1H-imidazo[4,5-c]pyridine. *J. Med. Chem.* **1985**, *28* (6), 717–727.

(13) Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Hayes, J. S. Structure-activity relationships of arylimidazopyridine cardiotonics; synthesis and inotropic activity of

benzthienyl- and naphthyl-substituted imidazopyridines and purines. *Eur. J. Med. Chem.* **1986**, *21* (3), 223−229.

(14) Honerjaeger, P.; Klockow, M.; Schoensteiner, G.; Jonas, R. Imidazopyridines: roles of pyridine nitrogen position and methyl-sulfinyl oxygen for in vitro positive inotropic mechanism and chronotropic activity. *J. Cardiovascular Pharm.* **1989**, *13* (5), 673−81.

(15) Hlavac, J.; Soural, M.; Krchnak, V. Practical aspects of combinatorial solid-phase synthesis. In *Solid-Phase Organic Synthesis*; Toy, P. H., Lam, Y., Eds.; Wiley: New York, 2012; pp 95−130.

(16) Zajdel, P.; Pawłowski, M.; Martinez, J.; Subra, G. *Comb. Chem. High Throughput Screen.* **2009**, *12* (7), 723−739.

(17) Legraverend, M.; Ludwig, O.; Bisagni, E.; LeClerc, S.; Meijer, L.; Giocanti, N.; Sadri, R.; Favaudon, V. Synthesis and in vitro evaluation of novel 2,6,9-trisubstituted purines acting as cyclin-dependent kinase inhibitors. *Bioorg. Med. Chem.* **1999**, *7* (7), 1281−1293.

(18) Di Lucrezia; Gilbert, I. H.; Floyd, C. D. Solid Phase Synthesis of Purines from Pyrimidines. *J. Comb. Chem.* **2000**, *2* (3), 249−253.

(19) Makara, G. M.; Ewing, W.; Ma, Y.; Wintner, E. Synthesis of Bicyclic Pyrimidine Derivatives as ATP Analogues. *J. Org. Chem.* **2001**, *66* (17), 5783−5789.

(20) Hammarström, L. G. J.; Smith, D. B.; Talamas, F. X.; Labadie, S. S.; Krauss, N. E. Utility of 4,6-dichloro-2-(methylthio)-5-nitro-pyrimidine. An efficient solid-phase synthesis of olomoucine. *Tetrahedron Lett.* **2002**, *43* (45), 8071−8073.

(21) Wang, S. S. *p*-Alkoxybenzyl Alcohol Resin and *p*-Alkoxybenzy-loxycarbonylhydrazide Resin for Solid Phase Synthesis of Protected Peptide Fragments. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.

(22) Rink, H. Solid-phase synthesis of protected peptide fragments using a trialkoxy-diphenyl-methylester resin. *Tetrahedron Lett.* **1987**, *28*, 3787−3790.

(23) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. Backbone Amide Linker (BAL) Strategy for Solid-Phase Synthesis of C-Terminal-Modified and Cyclic Peptides[1,2,3]. *J. Am. Chem. Soc.* **1998**, *120*, 5441−5452.

(24) Hanessian, S.; Xie, F. Polymer-bound p-alkoxybenzyl trichlor-oacetimidates: reagents for the protection of alcohols as benzyl ethers on a solid phase. *Tetrahedron Lett.* **1998**, *39* (8), 733−736.

(25) Laborde, E.; Peterson, B. T.; Robinson, L. Traceless, Self-Cleaving Solid- and Solution-Phase Parallel Synthesis of 3,4,7-Trisubstituted 3,4-Dihydroquinoxalin-2-ones. *J. Comb. Chem.* **2001**, *3* (6), 572−577.

(26) Kaplanek, R.; Krchnak, V. Fast and effective reduction of nitroarenes by sodium dithionite under PTC conditions: application in solid-phase synthesis. *Tetrahedron Lett.* **2013**, *54* (21), 2600−2603.

(27) Vanden Eynde, J. J.; Delfosse, F.; Lor, P.; Van Haverbeke, Y. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, a mild catalyst for the formation of carbon-nitrogen bonds. *Tetrahedron* **1995**, *51* (20), 5813−5818.

(28) Izumi, T.; Sakaguchi, J.; Takeshita, M.; Tawara, H.; Kato, K. I.; Dose, H.; Tsujino, T.; Watanabe, Y.; Kato, H. 1H-imidazo[4,5-c]-quinoline derivatives as novel potent TNF-+- suppressors: synthesis and structure-activity relationship of 1-, 2-and 4-substituted 1H-imidazo[4,5-c]quinolines or 1H-imidazo[4,5-c]pyridines. *Bioorg. Med. Chem.* **2003**, *11* (12), 2541−2550.

(29) Crey-Desbiolles, C.; Kotera, M. Synthesis of 3-deaza-3-nitro-2′-deoxyadenosine. *Bioorg. Med. Chem.* **2006**, *14* (6), 1935−1941.