Synthesis of benzo[1,2-*d*;3,4-*d′*]diimidazole and 1*H*-pyrazolo[4,3-*b*]pyridine as putative A_{2A} receptor antagonists

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Received 21st May 2007, Accepted 4th July 2007
First published as an Advance Article on the web 13th July 2007
DOI: 10.1039/b707599e

The synthesis and the binding affinity for the putative adenosine receptor antagonist 6-methyl-7-[1,2,3]triazol-2-yl-1,6-dihydrobenzo[1,2-*d*;3,4-*d′*]diimidazole (10) and 5-oxazol-2-yl-1*H*-pyrazolo[4,3-*b*]pyridin-3-ylamine (16) are reported. The title compounds were prepared from commercially available 1-chloro-2,4-dinitrobenzene (1) and 2-chloro-6-methoxy-3nitropyridine (11), respectively, but proved devoid of affinity for the adenosine A_1 and A_{2A} receptors.

Introduction

Adenosine modulates a great variety of biological functions both in the nervous system and peripheral tissues.[1] At least four adenosine receptor subtypes, A_1, A_2 (A_{2A}, A_{2B}), and A_3 have been identified.[2] There is evidence that potent and selective A_{2A} receptor antagonists can be useful for the treatment of neurodegenerative disorders, such as Parkinson's disease.[3–5] In this scenario, we reported the synthesis of 2-*n*-butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine and analogues and their A_{2A} receptor antagonist properties.[6] In connection with our ongoing studies on a new heterocyclic scaffold for A_{2A} receptor antagonists, we designed and synthesized 6-methyl-7-[1,2,3]triazol-2-yl-1,6-dihydrobenzo[1,2-*d*;3,4-*d′*]diimidazole (**10**) and 5-oxazol-2-yl-1*H*-pyrazolo[4,3-*b*]pyridin-3-ylamine (**16**) to explore their A_{2A} affinity and intrinsic activity. The two structures contain the pharmacophoric groups required for interaction with the A_{2A} receptor. The present paper describes the synthesis of **10** and **16** from cheap, commercially available starting materials, along with their biological activities.

Results and discussion

Unlike symmetric benzo[1,2-*d*;3,4-*d′*]diimidazoles, which are adequately reported in the literature,[7,8] very few examples of unsymmetric derivatives are known. A limited and non-general synthetic procedure for the synthesis of unsymmetric dialkyl derivatives employed 4-nitro-5-amino-2,1,3-benzothiadiazole,[9] which, *via* a sequence of reduction–cyclization–reduction–cyclization with two different alkyl carboxylic acids, furnished 2,5-dialkylbenzo[1,2-*d*;3,4-*d′*]diimidazoles.[10] This method cannot be used for compound **10**, because of the leaving group properties of the [1,2,3]triazole group of the [1,2,3]triazole-2-carboxylic acid or [1,2,3]triazole-2-carbaldehyde required for the cyclization step. We resorted therefore to the alternative procedures that are reported here.

The synthesis of 6-methyl-7-[1,2,3]triazol-2-yl-1,6-dihydrobenzo[1,2-*d*;3,4-*d′*]diimidazole (**10**) is described in Scheme 1. *N*1-Methyl-4-nitrobenzene-1,2-diamine (**3**) was prepared from commercially available 1-chloro-2,4-dinitrobenzene according to the literature.[11,12] Annelation of **3** with triethyl orthoformate produced 1-methyl-5-nitro-1*H*-benzoimidazole (**4**).[13] Chlorination of **4** with lithium diisopropylamide–*N*-chlorosuccinimide and reduction with tin in hydrochloric acid gave **6**.[14] Nitration of **6** using sodium nitrate in trifluoroacetic acid[15] and reduction with tin in hydrochloric acid afforded **8**. Cyclization of **8** with triethyl orthoformate gave **9**, that was substituted with 1*H*-1,2,3-triazole.[16] The reaction gave a mixture of two regioisomers (1-triazole and 2-triazole derivatives) with a total yield of 80%. Because of similar *R*f values of these compounds, it was not possible to purify them by flash chromatography (eluent: ethyl acetate–methanol 95 : 5). However, under these conditions, fractions enriched in the 2-triazole derivative were obtained. The fractions containing the mixture of the two regioisomers were treated with a solution of hydrobromic acid (48% in water) at room temperature in chloroform. Under these conditions, the 1-triazole derivative yielded degradation products, whereas the 2-triazole derivative (**10**) was stable. Compounds **9** and **10** exist in two tautomeric species that can be observed by ^{1}H NMR (DMSO-d6 at *ca.* 0.0042 M).[10,17]

Compound **16** is based on a 3-aminopyrazole moiety, a well-known adenino mimetic pharmacophore present in several classic inhibitors.[18–20] The $NH_2C{=}N{-}NH$ pattern of the 3-aminopyrazole moiety was introduced *via* the single-step procedure where the amino group was directly converted to aminopyrazole by sequential diazotation–reduction–annelation, whereas a typical procedure makes use of hydrazine as a source of dinitrogen.[21]

Regioselective introduction of the C-2 unsubstituted oxazole (1,2,3-triazole analogue) was achieved by a palladium(0) catalyzed cross-coupling reaction.[22] All the other reported methods of construction of the unsubstituted oxazole ring failed on our substrate.[23–25]

The synthesis of 5-oxazol-2-yl-1*H*-pyrazolo[4,3-*b*]pyridin-3-ylamine (**16**) is described in Scheme 2. The 6-methoxy-3-nitropyridine-2-carbonitrile (**12**), obtained from commercially available 2-chloro-6-methoxy-3-nitropyridine (**11**) and copper(I) cyanide,[26] gave 6-chloro-3-nitropyridine-2-carbonitrile (**13**) under Vilsmeier–Haack conditions.[27] Reaction of **13** with oxazol-2-yl-zinc chloride, prepared *in situ* by addition of excess zinc chloride

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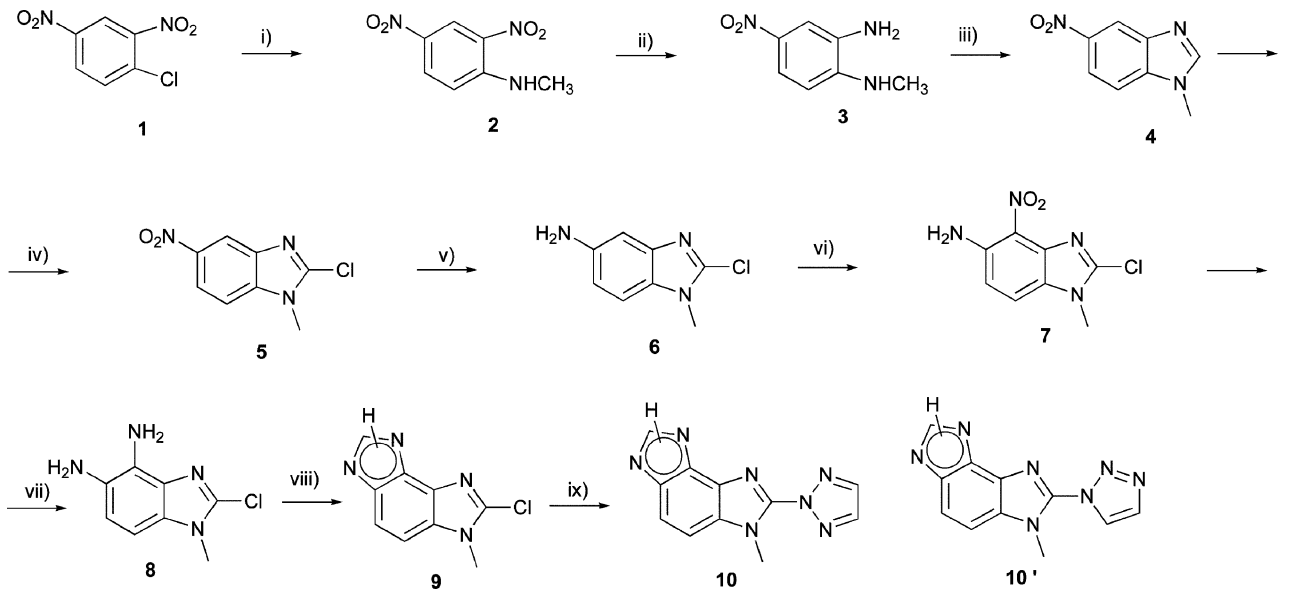
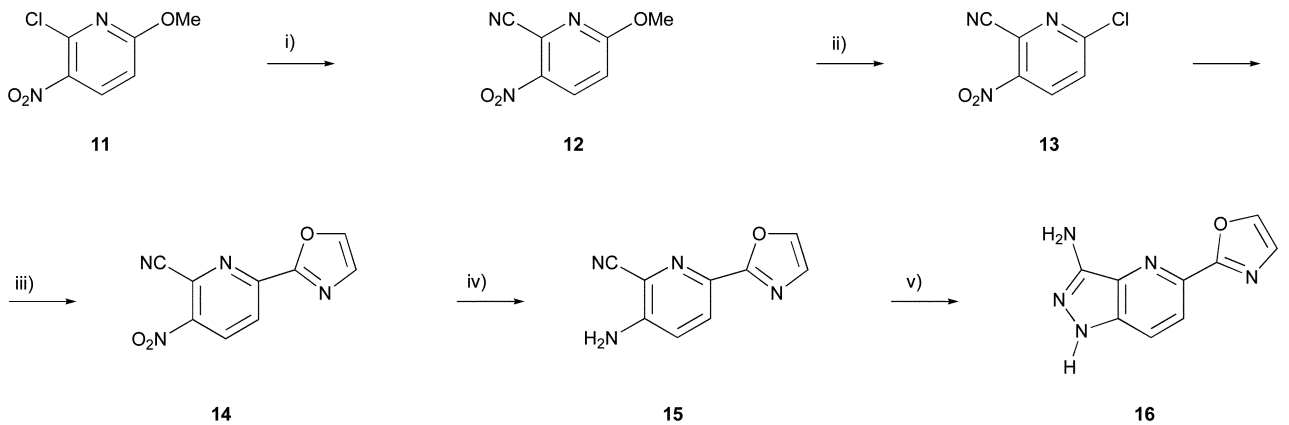


Scheme 1 *Reagents and conditions:* (i) EtOH, CH_3NH_2, rt, 15 h; (ii) CH_3CN, TEA, Pd/C, HCOOH, 80 °C, 3 h; (iii) DMF, $CH(OEt)_3$, HCl 12 N, rt, 1 h; (iv) (1) THF, LDA, −78 °C, 1 h, (2) NCS, rt, 10 min; (v) HCl 12 N, Sn, 90 °C, 1 h; (vi) CF_3COOH, $NaNO_3$, 0 °C, 3 h, rt, 6 h; (vii) HCl 12 N, Sn, 90 °C, 1 h; (viii) DMF, $CH(OEt)_3$, HCl 12 N, 0 °C, 1 h, rt, 3 h; (ix) DMF, NaH, 1*H*-1,2,3-triazole, 100 °C, 20 h.



Scheme 2 *Reagents and conditions:* (i) DMF, CuCN, 90 °C, 5 h; (ii) DMF, $POCl_3$, 95–99 °C, 42 h; (iii) THF, oxazole, BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, 90 °C, 4 h; (iv) MeOH, Fe, HCl 1 M, 60 °C, 1 h; (v) (1) HCl 37%, 0 °C, 2 min; (2) $NaNO_2$, 0 °C, 15 min; (3) $SnCl_2 \cdot 2H_2O$–HCl 37%, 80 °C, 2 h.

to oxazol-2-lithium, in the presence of palladium(0) catalyst, gave 3-nitro-6-oxazol-2-pyridine-2-carbonitrile (**14**). Reduction of **14** with Fe powder in hydrochloric acid afforded **15**. Compound **16** was obtained by sequential treatment of **15** with sodium nitrite in aqueous hydrochloric acid and reduction with tin(II) chloride.[28]

Table 1 reports the affinity [*K*i (nM)] values of compounds **10** and **16** for the A_1, and cloned human A_{2A} receptors (h-A2A), expressed in CHO-K1 (A_1) and HEK-293 (A_{2A}) cells (human embryo kidney cells). Radioligand [3*H*]-DPCPX was used for competition binding assays on A_1 receptors whereas [3*H*]-CGS21680 was used for h-A2A.[6] Compounds **10** and **16** displayed unsatisfactory affinity for the adenosine A_{2A} receptor.

Conclusions

In summary, we have designed, synthesized and biologically evaluated compounds **10** and **16**. Even though low affinity bindings resulted for these compounds, a new and reliable synthetic procedure for the preparation of a new and interesting heterocyclic scaffold was reported.

Table 1 Affinity *K*i (nM) and selectivity for the adenosine receptors

Compounds	A_{2A}	A_1	A_1–A_{2a}
10	3374.7	2445	0.72
16	>10 000	>10 000	

*K*i values represent replicate determinations and SEM are within ±20%.

Experimental

General comments

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent.

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Coupling constants (J values) are given in Hertz (Hz). EI-MS spectra (70 eV) were taken on a Fisons Trio 1000. Molecular ions (M+) and base peaks only are given. Melting points were determined on a Büchi SMP-510 capillary melting point apparatus and are uncorrected. Column chromatography purifications were performed in flash conditions using Merck 230–400 mesh silica gel. Thin-layer chromatography (TLC) was carried out with silica gel plates. Elemental analyses were performed by REDOX, Milan, Italy, and were within ±0.4 of the theoretical values (C,H,N). The solvents used for purification were purchased from Carlo Erba (Italy) with the exception of *N*,*N*-dimethylformamide and dichloromethane that were purchased from Fluka. The reactants were purchased from Aldrich, Fluka and Lancaster. Binding experiments were carried out as previously reported.[6]

(2,4-Dinitrophenyl)methylamine (2). Methylamine (40% w/w solution; 34 mL) was added to a solution of 1-chloro-2,4-dinitrobenzene (**1**) (12.3 g, 61 mmol) in ethanol (120 mL), at 0 °C. The mixture was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure and the brown oil residue was treated with hot water. The precipitate was filtered and dried on a stove to yield 12.1 g (100%) of **2**, mp 171 °C; ^{1}H NMR ($CDCl_3$) δ 3.17 (d, 3H, $J = 5.2$ Hz), 6.94 (d, 1H, $J = 9.5$ Hz), 8.32 (dd, 1H, $J = 2.7$ and 9.5 Hz), 8.56 (br s, 1H), 9.16 (d, 1H, $J = 2.7$ Hz); ms: m/e 197 (M+), 167, 105. Anal. Calcd. for $C_7H_7N_3O_4$: C, 42.72; H, 3.58; N, 21.31. Found: C, 42.72; H, 3.27; N, 21.22%.

***N*1-Methyl-4-nitrobenzene-1,2-diamine (3).** Pd/C (10%; 0.67 g) was added to a solution of (2,4-dinitrophenyl)methylamine (**2**) (12.14 g, 60.9 mmol) in acetonitrile (35 mL) and triethylamine (36.4 mL). The mixture was cooled to −15 °C and then formic acid (11.1 mL) in acetonitrile (35 mL) was added. The mixture was refluxed for 3 h and then the solvent was evaporated under reduced pressure to yield 10 g (99%) of **3** as a red liquid, ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3H), 6.51 (d, 1H, $J = 8.8$ Hz), 7.59 (d, 1H, $J = 2.6$ Hz), 7.83 (dd, 1H, $J = 2.6$ and 8.8 Hz); ms: m/e 167 (M+), 137, 121, 105, 94.

General procedure for the annelation of 3 and 8 to give 4 and 9. Hydrochloric acid (12 N solution, 1.7 mL) was added to a solution of **3** or **8** (15.2 mmol) in triethyl orthoformate (97 mL) and *N*,*N*-dimethylformamide (added with stirring until the turbidity disappeared). The mixture was stirred at room temperature for 12 h, under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the brown oily residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 2 : 8) to give **4** and **9** in 85% and 100% yield, respectively.

1-Methyl-5-nitro-1*H*-benzoimidazole (4). The compound was obtained as a white solid, mp 211–215 °C; ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H), 7.47 (d, 1H, $J = 8.9$ Hz), 8.07 (s, 1H), 8.28 (d, 1H, $J = 8.9$ Hz), 8.74 (s, 1H); ms: m/e 177 (M+), 147, 131, 116. Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.02; H, 4.03; N, 23.98%.

7-Chloro-6-methyl-1,6-dihydrobenzo[1,2-*d*;3,4-*d*′]diimidazole (9). The compound was obtained as a white solid, mp 224–230 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 7.20 (d, 1H, $J = 8.7$ Hz), 7.71 (d, 1H, $J = 8.7$ Hz), 7.96 (br, 1H), 8.04 (s, 1H); ms: m/e 208–206 (M+), 193–191. Anal. Calcd. for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.11; H, 3.72; N, 26.85%.

2-Chloro-1-methyl-5-nitro-1*H*-benzoimidazole (5). 2 M lithium diisopropylamide in THF–heptane–ethylbenzene (1.2 mL, 2.4 mmol) was added dropwise to a solution of **4** (1.33 mmol, 235 mg) in anhydrous THF (3.3 mL), under a nitrogen atmosphere at −78 °C. The solution was stirred at this temperature for 60 min, and then *N*-chlorosuccinimide (2.65 mmol, 353 mg) was added. This solution was stirred at room temperature for 10 min and then a saturated ammonium chloride solution was added. The mixture was extracted with dichloromethane, the organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 1 : 1) to yield 210 mg (75%) of **5**, mp: undeterminable—rubber-like substance; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.40 (d, 1H, $J = 8.9$ Hz), 8.28 (dd, 1H, $J = 2.0$ and 8.9 Hz), 8.61 (d, 1H, $J = 2.0$ Hz); ms: m/e 213–211 (M+), 183–181, 167–165, 155–153, 130.

General procedure for the reduction of 5 and 7 to give 6 and 8. A solution of **5** or **7** (8.51 mmol) in hydrochloric acid (12 N solution, 7 mL) was heated to 90 °C. Tin powder (3 g, 25.3 mmol) was added in five portions over a period of one minute. This solution was stirred at 90 °C for 15 min, cooled at 0 °C, diluted with water (100 mL) and basified with 30% sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure.

2-Chloro-1-methyl-1*H*-benzoimidazol-5-ylamine (6). The crude product obtained from the reduction of **5** was purified by flash chromatography on silica gel (ethyl acetate) to yield 1.4 g (93%) of **6**, mp 145–147 °C; ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 3H), 6.72 (dd, 1H, $J = 2.1$ and 8.5 Hz), 6.99 (d, 1H, $J = 2.1$ Hz), 7.08 (d, 1H, $J = 8.5$ Hz); ms: m/e 183–181 (M+), 168–166, 131. Anal. Calcd. for $C_8H_8ClN_3$: C, 52.90; H, 4.44; N, 23.14. Found C, 52.73; H, 4.22; N, 22.95%.

2-Chloro-1-methyl-1*H*-benzoimidazole-4,5-diamine (8). The crude product obtained from the reduction of **7** was used in the following reaction without further purification, to yield a rubber like substance of undeterminable mp; ms: m/e 198–196 (M+), 183–181, 154.

2-Chloro-1-methyl-4-nitro-1*H*-benzoimidazol-5-ylamine (7). A mixture of 2-chloro-1-methyl-1*H*-benzoimidazol-5-ylamine (**6**) (100 mg, 0.552 mmol), sodium nitrate (52 mg, 0.60 mmol) and trifluoroacetic acid (2 mL) was stirred at 0 °C for 3 h and room temperature for 6 h. The mixture was poured into ice water and basified (pH 10) with 30% sodium hydroxide solution. The aqueous phase was extracted with ethyl acetate, and the organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 1 : 1) to yield 80 mg (67%) of **7**, mp 237–241 °C; ^{1}H NMR ($CDCl_3$): δ 3.79 (s, 3H), 6.2 (br, 2H), 6.75 (d, 1H, $J = 8.9$ Hz), 7.3 (d, 1H, $J = 8.8$ Hz); ms: m/e 228–226 (M+), 211–209, 198–196, 180. Anal. Calcd. for $C_8H_7ClN_4O_2$: C, 42.40; H, 3.11; N, 24.72. Found C, 42.65; H, 3.27; N, 24.48%.

6(3)-Methyl-7(2)-[1,2,3]triazol-2-yl-1(3),6-dihydrobenzo[1,2-*d*;3,4-*d*′]diimidazole (10). 1*H*-1,2,3-triazole (0.18 mL, 2.5 mmol)

was added dropwise to a suspension of anhydrous *N*,*N*-dimethylformamide (2 mL) and sodium hydride (80% in paraffin, 92 mg, 2.5 mmol) under a nitrogen atmosphere. The mixture was stirred for 1 h. A solution of **9** (1.7 mmol, 350 mg) in anhydrous *N*,*N*-dimethylformamide (5 mL) was added, dropwise, and the resulting mixture stirred at 100 °C for 20 h.

The solvent was removed under reduced pressure, and water was added to the residue. The aqueous phase was extracted with dichloromethane, and the collected organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Based on HPLC analysis, the ratio between the two triazole regioisomers was 30 : 70 (**10**–**10′**). The residue was purified by flash chromatography on silica gel (ethyl acetate–methanol 95 : 5) (under these conditions, it was possible to obtain a fraction enriched in the 2-triazole derivative). The fractions containing the mixture of the two regioisomers were dissolved in chloroform and then 6 drops of a solution of hydrobromic acid (48% w/w in water) were added. The mixture was stirred at room temperature for 5 min (under these conditions, the 1-triazole derivative yielded degradation products). The solution was diluted with water and rendered alkaline (pH 10) with 30% sodium hydroxide solution at 0 °C. The aqueous phase was extracted with ethyl acetate, and the organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane–acetone 98 : 2) to give 83 mg (25%) of **10**, mp 280–282 °C; ^{1}H NMR ($CDCl_3$): δ 4.15 (s, 3H), 7.37 (d, 1H, $J = 8.9$ Hz), 7.87 (d, 1H, $J = 8.9$ Hz), 8.03 (s, 2H), 8.10 (s, 1H); ^{1}H NMR (DMSO-d6, 0.0042 M, 298 K): δ 3.91 (s, 3H), 3.95 (s, 3H), 7.4–7.7 (m, 4H), 8.20 (s, 1H), 8.25 (s, 1H), 8.35 (s, 4H), 12.71 (br, 1H), 13.26 (br, 1H); ms: *m*/*e* 239 (M+), 184, 158.

Anal. Calcd. for $C_{11}H_9N_7$: C, 55.22; H, 3.79; N, 40.98. Found C, 54.89; H, 4.02; N, 41.17%.

6-Methoxy-3-nitropyridine-2-carbonitrile (12). Copper(I) cyanide (5.7 g, 63.49 mmol) was added to a solution of 2-chloro-6-methoxy-3-nitropyridine (**11**) (4 g, 21.16 mmol) in *N*,*N*-dimethylformamide (40 mL). The mixture was stirred at 90 °C for 5 h. The solution was poured into a water–ethyl acetate (100 : 100) mixture and stirred for 5 min. The solution was filtered over Celite. The layers were separated, the organic phase washed with water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 8 : 2) to yield 3.2 g (84%) of **12**, mp 85–87 °C; ^{1}H NMR ($CDCl_3$): δ 4.12 (s, 3H), 7.10 (d, 1H, $J = 9.2$ Hz), 8.45 (d, 1H, $J = 9.2$ Hz); ms: *m*/*e* 179 (M+), 149, 133, 118. Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.46. Found C, 47.07; H, 2.69; N, 23.07%.

6-Chloro-3-nitropyridine-2-carbonitrile (13). Phosphoryl chloride (338 mg, 2.2 mmol) was added to a solution of **12** (179 mg, 1 mmol) in dry *N*,*N*-dimethylformamide (16 mL) at 0 °C. The mixture was stirred at this temperature for 1 h and then heated at 95–99 °C for 42 h; 1 mmol of phosphoryl chloride was added every 14 h. The solution was cooled to 0 °C, quenched by adding saturated sodium acetate solution and warmed in a water bath for 3 min. After cooling, the mixture was extracted with ethyl acetate and the organic phases were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane–dichloromethane 4 : 6) to yield 110 mg (60%) of **13**, mp 118–120 °C; ^{1}H NMR ($CDCl_3$): δ 7.80 (d, 1H, $J = 7.2$ Hz), 8.58 (d, 1H, $J = 7.2$ Hz); ms: *m*/*e* 185–183 (M+), 139–137, 125, 101. Anal. Calcd. for $C_6H_2ClN_3O_2$: C, 39.26; H, 1.10; N, 22.89. Found C, 39.64; H, 1.32; N, 22.74%.

3-Nitro-6-oxazol-2-ylpyridine-2-carbonitrile (14). 2.5 M *n*-butyl lithium in hexane (0.15 mL, 0.38 mmol) was added to a deoxygenated, cooled (−70 °C) solution of oxazole (25 µL, 0.38 mmol) in THF (2 mL). The mixture was stirred at −70 °C for 30 min and then 1 M zinc chloride in ether (1.14 mL, 1.14 mmol) was added. The reaction was warmed to 0 °C and maintained at this temperature for 1 h. To this mixture was added a solution of **13** (70 mg, 0.38 mmol) in deoxygenated THF (2 mL) and tetrakis(triphenylposphine)palladium(0) [$Pd(PPh_3)_4$] (44 mg, 0.038 mmol). The resulting mixture was refluxed for 4 h. The mixture was then cooled, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate 6 : 4) to give 16 mg (20%) of **14**, mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.98 (s, 1H), 8.59 (d, 1H, $J = 8.8$ Hz), 8.74 (d, 1H, $J = 8.8$ Hz); ms: *m*/*e* 216 (M+), 186, 170. Anal. Calcd. for $C_9H_4N_4O_3$: C, 50.01; H, 1.87; N, 25.92. Found C, 49.87; H, 2.03; N, 26.13%.

3-Amino-6-oxazol-2-ylpyridine-2-carbonitrile (15). Powdered iron (1 mmol, 56 mg) was added to a solution of **14** (0.5 mmol, 108 mg) in methanol (2 mL) and hydrochloric acid (1 N solution, 9.8 mL). The mixture was stirred at 60 °C for 1 h and then basified (pH 10) with 1 N sodium hydroxide solution and filtered through a Celite cake, which was washed with several portions of ethyl acetate and methanol. The layers were separated, and the aqueous phase was extracted with additional ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure, to give a residue that was used for the following reaction without further purification, ^{1}H NMR ($CDCl_3$): δ 4.74 (br, 2H), 7.23 (d, 1H, $J = 8.6$ Hz), 7.25 (s, 1H), 7.78 (s, 1H), 8.12 (d, 1H, $J = 8.6$ Hz); ms: *m*/*e* 186 (M+), 158, 105.

5-Oxazol-2-yl-1*H*-pyrazolo[4,3-*b*]pyridin-3-ylamine (16). A mixture of **15**, hydrochloric acid (12 N solution, 2 mL) and water (1 mL) was stirred until a complete solution was obtained. The solution was cooled to 0 °C and then a pre-chilled (0 °C) solution of sodium nitrate (40 mg, 0.57 mmol) in water (1 mL) was added dropwise. After 15 min, a pre-chilled solution of tin(II) chloride dihydrate (283 mg, 1.25 mmol) in hydrochloric acid (12 N solution, 2 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 h and then heated at 80 °C for 2 h. The mixture was cooled, basified with 30% sodium hydroxide solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate) to yield 20 mg (26%) of **16**, mp > 250 °C degradation (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 4.69 (br, 2H), 6.99 (s, 1H), 7.33 (s, 1H), 7.76 (d, 1H, $J = 8.9$ Hz), 7.83 (s, 1H), 8.18 (d, 1H, $J = 8.9$ Hz); ms: *m*/*e* 201 (M+), 172. Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found C, 53.89; H, 3.64; N, 35.03%.

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