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Synthesis and functionalisation of 1H-pyrazolo[3,4-*b*]pyridines involving copper and palladium-promoted coupling reactions

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Abstract—A convenient route to novel 3-iodo-1H-pyrazolo[3,4-*b*]pyridines via iododediazonation of 3-amino-1H-pyrazolo[3,4-*b*]pyridines, which are obtained by copper-catalysed cyclisation of 2-chloro-3-cyanopyridine with hydrazines. We describe also efficient coupling reactions from 3-iodo derivatives with various reagents according to Suzuki, Heck, Stille, and Sonogashira conditions.
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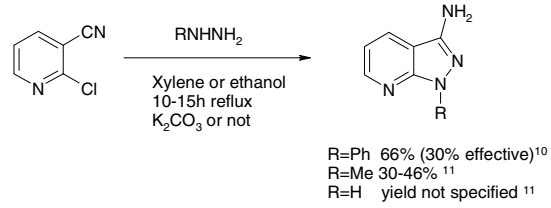
Indoles and indazoles are known to be pharmacophoric elements in numerous active compounds, natural or not.[1–6]

Interest in the synthesis of condensed pyrazoles has recently revived because of the wide variety of their biological properties.[7–9]

However, few publications are devoted to chemistry of pyrazolo[3,4-*b*]pyridines[10,11] as indole or indazole isosteres. We report here the synthesis of 3-aminopyrazolo[3,4-*b*]pyridines by copper-mediated cyclisation of 2-chloronicotinonitrile with hydrazines.

Aiming to extend pyrazolo[3,4-*b*]pyridine libraries, we also describe a versatile pathway leading to 3-alkylated pyrazolo[3,4-*b*]pyridines via palladium-catalysed coupling reactions involving 3-iodopyrazolo[3,4-*b*]pyridines, which are obtained by iododediazonation of 3-aminopyrazolo[3,4-*b*]pyridines.

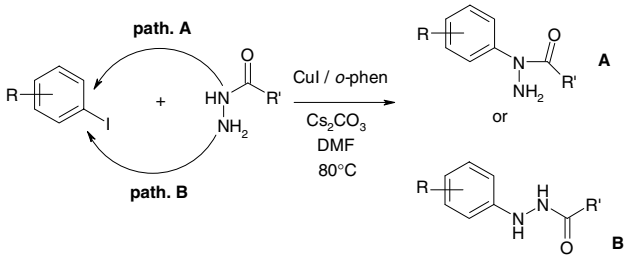
The unique way to prepare 3-aminopyrazolo[3,4-*b*]pyridines[10,11] starts with 2-chloronicotinonitrile and hydrazines but requires harsh conditions and proceeds in poor yield (66% yield with phenylhydrazine in xylene according to Kuczynski,[10] in our hands we have obtained only 30%). Chemical variation in position 1 is also weakly representated because only three substituents were investigated (Scheme 1).



Scheme 1. Previous synthesis of 3-aminopyrazolo[3,4-*b*]pyridines.

We present here a modified procedure using copper catalyst based on Buchwald and co-worker's[12] work. They have reported efficient amination of aryl iodides with acylhydrazides using copper(I) iodide/*ortho*-phenanthroline as catalyst in DMF. However two regioisomers (**A** and **B**) may be obtained depending on the substitution on the benzene ring (Scheme 2).

We found that reaction of 2-chloro-3-cyanopyridine **1** with hydrazines using the above method gave only **A**



Scheme 2. Copper-catalysed amination of aryl iodides.

Keywords: 1H-pyrazolo[3,4-*b*]pyridines.
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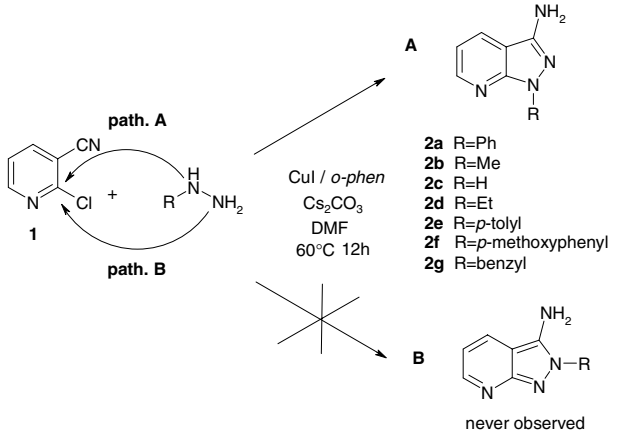
isomer (Scheme 3). Structures were confirmed by comparison of the ^{1}H NMR spectra with literature[11] for described compounds. Note that **B** isomer type is not known, except for R = Me, which was reported in a Japanese patent[13] application.

Reaction of 2-chloro-3-cyanopyridine **1** with excess hydrazines, 5/10 mol% of CuI/*o*-phenanthroline and cesium carbonate in DMF overnight afforded 1-substitued-3-amino-pyrazolo[3,4-*b*]pyridines in fair yields[14] (Table 1).

Strongly nucleophilic hydrazines such as aliphatic derivatives gave higher yields and cleaner reactions than aromatic ones. Particularly deactivated hydrazines such as *p*-cyanophenylhydrazine and 2,4-dinitrophenylhydrazine have, respectively, shown no reaction or degradation.

Treatment of 3-amino-pyrazolo[3,4-*b*]pyridines (**2a**,**b**) with sodium nitrite[15] in aqueous acidic conditions at 0 °C lead to the diazonium salt (not isolated), which was decomposed by potassium iodide to give 3-iodo-pyrazolo[3,4-*b*]pyridines[16] (**3a**,**b**). If R = H (**3c**) complete degradation of the starting material occurred. To prepare missing product **3c** we applied Rault's method,[17] used in the benzopyrazole series, to our pyridinic system. Unfortunately diazotization of 2-aminopicoline **2′** failed to give pyrazolo[3,4-*b*]pyridine **3′**. No trace of **3′** was isolated and **2′** was recovered unchanged (Scheme 4).

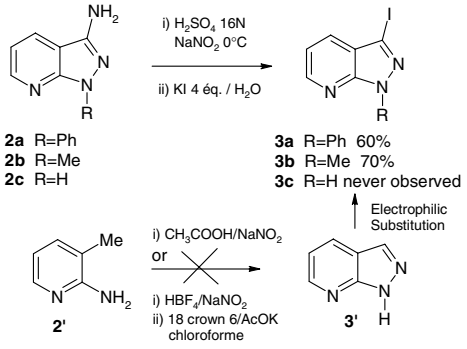
Compounds (**4a**–**7a** and **4b**–**7b**) were prepared from 3-iodopyrazolo[3,4-*b*]pyridines (**3a**,**b**) following Stille,[18] Heck,[19] Sonogashira[20] or Suzuki[21] conditions (Scheme 5).



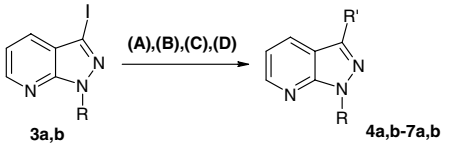
Scheme 3. Synthesis of pyrazolo[3,4-*b*]pyridines.

Table 1. Cyclisation yields

	Product	% Yield
2a	R = Ph	50
2b	R = Me	93
2c	R = H	70
2d	R = Et	86
2e	R = *p*-tolyl	53
2f	R = *p*-methoxyphenyl	61
2g	R = benzyl	72



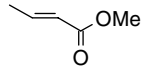
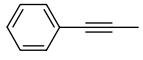
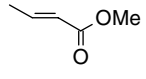
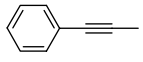
Scheme 4. Preparation of 3-iodo-pyrazolo[3,4-*b*]pyridines.



Scheme 5. Reagents and conditions: (**A**) (1-ethoxyvinyl)-tributyltin, $Pd(PPh_3)_4$, toluene, reflux 2 h; (**B**) methyl acrylate, $PdCl_2(dppf)_2$, *n*-Bu_4NI, DMF/TEA/H_2O, 50 °C, 2 h; (**C**) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, DMF/TEA, rt, overnight; (**D**) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, 75 °C, 1 h 30.

The transformations proceeded under quite mild conditions and reaction times were often short. The experiments lead to the expected compounds with excellent yields (Table 2) even for ethoxyvinyl products (**4a**,**b**), which are usually sensitive derivatives.

Table 2. Coupling yields

R	R′	Path	Compound	% Yield
Me		(**A**)	**4a**	80
Me		(**B**)	**5a**	82
Me		(**C**)	**6a**	92
Me		(**D**)	**7a**	80
Ph		(**A**)	**4b**	78
Ph		(**B**)	**5b**	86
Ph		(**C**)	**6b**	78
Ph		(**D**)	**7b**	73

In conclusion, we have improved the formation of pyrazolo[3,4-*b*]pyridine ring from 2-chloro-3-cyanopyridine and hydrazines using catalytic amounts of CuI/*o*-phenanthroline. We have also obtained new 3-iodopyrazolo[3,4-*b*]pyridines, extending the possibilities in this heterocycle chemistry. In this way, four classic types of cross-coupling palladium-mediated reactions were investigated successfully from the 3-iodo compounds.

Acknowledgements

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14. *General procedure for the preparation of 3-amino-pyrazolo[3,4-b]pyridines* (**2a**–**c**): 2-Chloronicotinonitrile **1** (1.4 mmol) was introduced into a 25 cm^3 flask then 0.07 mmol (5 mol%) of copper(I) iodide, 2.1 mmol of caesium carbonate and finally 0.16 mmol (10 mol%) of 1,10-phenanthroline. DMF (5 mL) was poured followed by 8.7 mmol of suitable hydrazine. The mixture was heated to 60 °C overnight. Water (10 mL) was introduced after cooling and the aqueous phase was extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified on silica gel column chromatography. *Compound* **2b**: 3-Amino-1-methyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$) δ_{ppm} 3.91 (s, 3H, CH_3); 4.21 (sl, 2H, NH_2); 6.92 (dd, 1H, H_5, $J = 4.4$, 8.1 Hz); 7.85 (dd, 1H, H_4, $J = 1.5$, 8.1 Hz); 8.43 (dd, 1H, H_6, $J = 1.5$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 32.9 (*C*H_3); 106.6 (C_{3a}), 114.2 (C_5); 128.7 (C_4), 145.5 (C_3); 149.1 (C_6); 150.8 (C_{7a}). MS $m/z = 148$ $(M+H)^+$.
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16. *General procedure for the preparation of 3-iodo-pyrazolo[3,4-b]pyridines* (**3a**,**b**): 3-Amino-pyrazolo[3,4-*b*]pyridine (3.4 mmol) in 10 mL of sulfuric acid 16 N were cooled to 0 °C then 3.5 mmol of sodium nitrite in 3 mL of water was added slowly at 0 °C. The medium was stirred 1 h at 0 °C then 13.5 mmol of potassium iodide in 10 mL of water was poured all at once. The mixture was heated to room temperature for 1 h then brought to pH = 7/8 using solid sodium carbonate and extracted with dichloromethane. The organic phase was washed with a saturated solution of sodium thiosulfate then dried over $MgSO_4$ and finally evaporated under reduced pressure. The crude residue was purified on silica gel column chromatography. *Compound* **3b**: 3-Iodo-1-methyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 4.19 (s, 3H, CH_3); 7.17 (dd, 1H, H_5, $J = 4.4$, 8.2 Hz); 7.81 (dd, 1H, H_4, $J = 1.6$, 8.2 Hz); 8.58 (dd, 1H, H_6, $J = 1.6$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 34.4 (*C*H_3), 89.2 (C_3); 117.4 (C_5); 120.5 (C_{3a}); 130.5 (C_4); 150.0 (C_6); 150.7 (C_{7a}). MS $m/z = 260$ $(M+H)^+$.
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18. See experimental section for Stille coupling: Aboul-Fadl, T.; Löber, S.; Gmeiner, P. *Synthesis* **2000**, 1727–1732.
Compound **4a**: 3-(1-Ethoxyvinyl)-1-methyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 1.47 (t, 3H, CH_2CH_3, $J = 7.2$ Hz); 4.01 (q, 2H, OCH_2, $J = 6.9$ Hz); 4.13 (s, 3H, NCH_3); 4.32 (d, 1H, C=C*H*, $J = 2.5$ Hz); 5.01 (d, 1H, C=C*H*, $J = 2.5$ Hz); 7.08 (dd, 1H, H_5, $J = 4.4$, 8.1 Hz); 8.29 (dd, 1H, H_4, $J = 1.5$, 8.1 Hz); 8.48 (dd, 1H, H_6, $J = 1.5$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 14.6 (CH_2CH_3), 34.1 (NCH_3); 63.3 (OCH_2); 83.4 (C=*C*H); 113.5 (C_{3a}); 117.0 (C_5); 131.5 (C_4); 139.5 (C_3); 148.8 (C_6); 151.0 (*C*=CH); 155.1 (C_{7a}). MS $m/z = 204$ $(M+H)^+$.
19. See experimental section for Heck coupling: Collot, V.; Varlet, D.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 4363–4366.
Compound **5a**: Methyl-3-(*E*)-(1-methyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-acrylate: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 3.83 (s, 3H, NCH_3); 4.17 (s, 3H, OCH_3); 6.71 (d, 1H, N=C–C*H*=C; $J = 16.0$ Hz); 7.21 (dd, 1H, H_5, $J = 4.4$, 8.1 Hz); 7.91 (d, 1H, =C*H*–COO, $J = 16.0$ Hz); 8.23 (dd, 1H, H_4, $J = 1.5$, 8.1 Hz); 8.57 (dd, 1H, H_6, $J = 1.5$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 34.4 (N*C*H_3); 51.9 (O*C*H_3); 114.4 (C_{3a}); 117.9 (C_5); 119.5 (*C*=C–C=O); 129.8 (C=*C*–C=O); 135.9 (C_4); 138.7 (C_3); 149.2 (C_6); 151.4 (C_{7a}); 167.3 (*C*=O). MS $m/z = 218$ $(M+H)^+$.
20. See experimental section of Ref. 17 for Sonogashira coupling. *Compound* **6a**: 1-Methyl-3-phenylethynyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 4.11 (s, 3H, NCH_3); 7.11 (dd, 1H, H_5, $J = 4.4$, 8.2 Hz); 7.10–7.39 (m, 3H, H_{arom}); 7.48–7.60 (m, 2H, H_{arom}); 8.10 (dd, 1H, H_4, $J = 1.6$, 8.2 Hz); 8.50 (dd, 1H, H_6, $J = 1.6$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 34.4 (N*C*H_3); 80.4 (C≡*C*Ph) 93.3 (*C*≡CPh); 117.2 (C_{3a}); 117.5 (C_5); 122.5 (C_{arom}); 127.2 (C_3); 128.5 (C_{arom}); 128.9 (C_{arom}); 129.9 (C_{arom}); 131.9 (C_4); 149.4 (C_6); 150.3 (C_{7a}). MS $m/z = 234$ $(M+H)^+$.
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Compound **7a**: 1-Methyl-3-phenyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$) δ_{ppm} 4.21 (s, 3H, NCH_3); 7.15 (dd, 1H, H_5, $J = 4.7$, 8.2 Hz); 7.38–7.53 (m, 3H, H_{arom}); 7.87–8.02 (m, 2H, H_{arom}); 8.31 (dd, 1H, H_4, $J = 1.2$, 7.8 Hz); 8.56 (dd, 1H, H_6, $J = 1.2$, 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ_{ppm} 34.1 (NCH_3); 113.6 (C_{3a}); 117.0 (C_5); 127.1 (C_{arom}); 128.4 (C_{arom}); 129.0 (C_{arom}); 130.5 (C_4); 133.3 (C_{arom}); 142.6 (C_3); 148.8 (C_6); 151.5 (C_{7a}). MS $m/z = 210$ $(M+H)^+$.