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Rapid synthesis of imidazo[4,5-*b*]pyridine containing polycyclics by means of palladium-catalyzed amidation of 2-chloro-3-nitropyridine

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ABSTRACT

Regioselective nucleophilic substitution of 2-chloro 3-nitropyridine with heterocyclic amides under Pd-catalyzed reaction conditions as described by Buchwald yielded imidazo [4,5-*b*] pyridine-containing polycyclics as novel scaffolds.

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Substituted benzimidazoles and structurally related compounds are of pharmacological and therapeutical interest.[1] In some cases, bioisosteric replacement within the benzimidazole scaffold leading to imidazo[4,5-*b*]pyridines resulted in improved properties as compared to the corresponding parent compound.[2] Their preparation resulted from reaction of a primary amine with 2-chloro-3-nitropyridine **1**. The resulting 2-aminopyridine intermediate was N-acylated (method a). Finally, the *N*-acyl 2-amino pyridine **2** was reduced and submitted to cyclization after an activation step involving a Brönsted[1,3], or Lewis acid[4] catalyst (Scheme 1).

This Letter presents a very straightforward method for preparing differently substituted imidazo [4,5-*b*] pyridines **4**. The target compounds mainly result from direct amidation (method b) of the highly electrophilic 2-chloro-3-nitropyridine **1** with various amides including primary, secondary, and cyclic amides using Pd-coupling reactions, as described recently by Buchwald.[5]

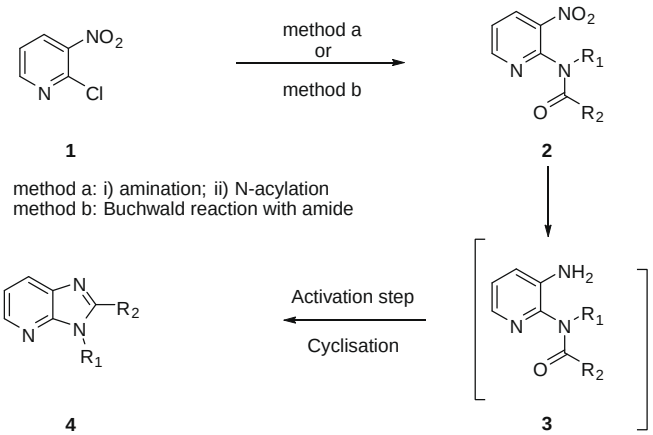
More recently, Buchwald[6,7] and co-workers reinvestigated the N-arylation of heterocyclic compounds containing a NHCO-moiety by using catalytic amounts of a commercially available copper catalyst.[8]

Despite the poor nucleophilic character of amides, when reacted with aryl halides, the reaction could be extended to sulfonamides, carbamates, and ureas by means of Xantphos as ligand and Cs_2CO_3 as the base in dioxane in the presence of $Pd(OAc)_2$ or $Pd_2(dba)_3$.[5]

A first set of model reactions was performed with **1** in refluxing dioxane under similar experimental conditions[9] as described by Buchwald[5] (Table 1).

The yields were satisfactory with primary amides ($R_1 = H$). Surprisingly a dramatic drop in reactivity was found with *N*-methylacetamide (entry 3), as no reaction could be also observed with the more electrophilic 2,6-dichloropyridine. Similar results were found by Buchwald within the aryl series, and were explained by steric hindrance deriving from the cis–trans geometry of the deprotonated amide, and its capacity to complex the palladium.[10] In contrary, cyclic amides, as secondary amides constrained in cis amide geometry, were found to be highly reactive (entries 4–9). However, the presence of a benzo ring in the dihydroquinolone led to a dramatic decrease in reactivity (compare entries 5 and 10), as a result of electronic or steric effects of the N-phenylamide system. A similar lack of activity was observed in the attempted N-arylation of various NH amide heterocycles by copper-catalyzed Ullmann condensation.[8]

The data listed in Table 1 highlighted specific electronic features combined with steric effects, which may lead to some interesting regio- or chemoselective *N*-arylation reactions. Various cyclic amides including five (compounds **2d**, **2f**, **2g**), six (compounds **2e**, **2h, 2j**), or seven (compound **2i**) membered-ring systems were



Scheme 1. Preparation of imidazo [4,5-*b*] pyridines **4**.

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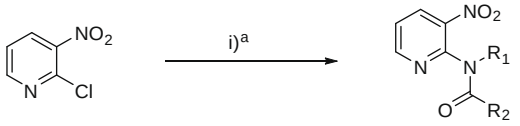
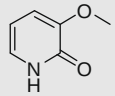
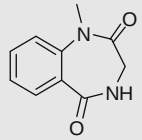
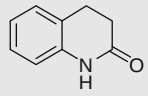
Table 1



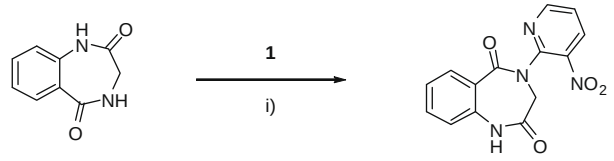
1 **2**

Entry	R_2CONHR_1		Compd	Yield[b] (%)
	R_1	R_2		
1	H	Me	**2a**	82
2	H	Ph	**2b**	65
3	Me	Me	**2c**	n.r.[c]
				
4	A = CH_2		**2d**	80[d]
5	A = $(CH_2)_2$		**2e**	72
6	A = O		**2f**	90
7	A = NMe		**2g**	60
8			**2h**	60
9			**2i**	85
10			**2j**	n.r.[c]

[a] $Pd(OAc)_2$/Xantphos, Cs_2CO_3, dioxane (100 °C, 16 h).[9]
[b] Non-optimized yields.
[c] n.r. no reaction.
[d] The reaction performed in similar experimental conditions (a), but without Pd/L catalysts gave less than 10% of **2d**.

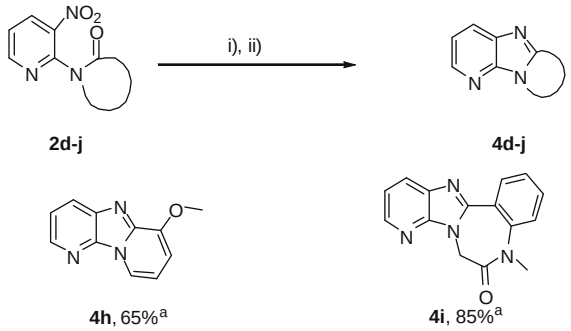
efficiently N-substituted under these conditions, even if they were presenting strong aromatic character (compound **2h**). In particular the very low reactivity of N-arylamide-containing heterocycles toward *N*-aryl substitution was observed in general (see entry 10). Surprisingly, the Buchwald reaction described here showed interesting regioselectivity, as illustrated by reaction of **1** with free NH-diamide heterocycles (see Scheme 2). When reacted with **1**, 1,4-benzodiazepin-2,5-dione **5** yielded a single regioisomer (compound **6**) in the reaction mixture. This result is in good agreement with the lack of reactivity observed with another cyclic N-phenylamide (see entry 10 in Table 1)

The nitro intermediates **2** were quantitatively reduced by means of iron in presence of ammonium chloride in a mixture of ethanol and water. The resulting crude amino intermediate was further submitted to cyclization using $SiCl_4$ as an efficient, low-cost



5 **6**, 52%

Scheme 2. Regio- and chemoselectivity of the reaction. (i) $Pd(OAc)_2$/Xantphos, Cs_2CO_3, dioxane (100 °C), 16 h.[11]



Scheme 3. Easy access to novel polyheterocyclic compounds. (i) Fe/NH_4Cl, EtOH, H_2O, (ii) $SiCl_4$, CH_2Cl_2 μ-waves, 10 min, 180 °C.

Lewis catalyst.[4] However, the reaction needed long reaction times (1–4 days) to complete the cyclization. This reaction could be also performed in 10 min after exposure to microwave irradiation at 180 °C. The overall yields (reduction and cyclization) was satisfactory to good (55–90%).[12]

Finally, depending on the amide-containing heterocycle (mono- or bicyclic compound), various imidazo pyridine-fused polycyclic compounds could be easily obtained in good yield. As typical examples given in Scheme 3, the preparation of the tricyclic imidazo pyridine **4h** constituted an interesting 'umpolung approach' of the recently described[13] Buchwald reaction of 2-chloro-3-iodopyridine (instead of **1** in our method) and 2-aminopyridine (instead of 3-methoxypyridin-2(1H)-one (entry 8) in our example) leading to a common dipyrido imidazole system (compound **4h**). Also, in another example involving an NH-amide bicycle (entry 9), the resulting tetracyclic compound **4i** could be prepared in good overall yield. A similar strategy may be extended to larger polycyclic compounds possessing a common fused imidazole ring at the junction of both reagents.

In conclusion, the search of novel polyheterocyclic scaffolds useful in medicinal chemistry led us to develop a methodology involving a highly electrophilic heteroarylchloride (i.e., 2-chloro-3-nitropyridine **1**) and various free NH-amide heterocycles including mono- and bicyclic systems. The reaction only needed two separate reaction steps, and generally the expected compound was obtained in satisfactory overall yield and possessed some additional functionalities for further substitutions.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.031.

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8. Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719.
9. Supplementary data available: Experimental procedures and spectral data. This material is available free of charge.*General procedure for the Buchwald reaction with the 2-chloro-3-nitropyridine*: In a flame-dried Schlenk tube, palladium acetate (0.016 mmol, 0.05 equiv), Xantphos (0.032 mmol, 0.1 equiv), and Cs_2CO_3 (0.480 mmol, 1.5 equiv) were introduced under Argon. The Schlenk tube was purged few minutes with Ar. A solution of 2-chloro-3-nitropyridine (**1**) (0.320 mmol, 1 equiv) and amide (0.384 mmol, 1.2 equiv) in dioxane (1 mL) was added. The Schlenk tube was purged 3 times with Ar. The mixture was stirred at 100 °C (16 h). The solution was filtered through a pad of Celite. The pad was washed with CH_2Cl_2. Water (5 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (Heptane/EtOAc) to obtain the desired compounds. 1-Methyl-3-(3-nitro-pyridin-2-yl)-imidazolidin-2-one (**2g**); yellow solid; TLC/R_f = 0.37 (cyclohexane/EtOAc 7/3); Yield : 60%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.93 (s, 3H, NC*H*$_3$), 3.61 (t, 2H, *J* = 7.4 Hz, C*H*$_2$NMe), 4.15 (t, 2H, *J* = 7.4 Hz, C*H*$_2$N), 7.16 (dd, 1H, *J* = 8.0 Hz, *J* = 4.7 Hz, Ar*H*), 8.18 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz, Ar*H*), 8.50 (dd, 1H, *J* = 4.7 Hz, *J* = 1.6 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 30.8 (CH_3), 42.1 (CH_2N), 43.7 (CH_2NMe), 118.3, 133.5, 138.5, 144.4, 150.6, 156.2 (CO); LRMS: *m/z* (APCI) 223.0 (MH^+. $C_9H_{10}N_4O_3H^+$ requires 223.0).
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11. *Preparation of 4-(3-nitropyridin-2-yl) -3,4-dihydro-1H-benzo[e] [1,4]diazepine-2,5-dione* (**6**)*:* In a flame-dried Schlenk tube, palladium acetate (0.016 mmol, 0.05 equiv), Xantphos (0.032 mmol, 0.1 equiv), and Cs_2CO_3 (0.480 mmol, 1.5 equiv) were introduced under Ar. The Schlenk tube was purged few minutes with Ar. A solution of 2-chloro-3-nitropyridine (**1**) (0.320 mmol, 1 equiv) and **5** (0.384 mmol, 1.2 equiv) in dioxane (1 mL) was added. The mixture was stirred at 100 °C (16 h). The solution was filtered through a pad of Celite. The pad was washed with CH_2Cl_2. The organic layers were combined and the solvents were evaporated. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc 4/6 to EtOAc) to obtain the coupled compound as a yellowish solid; TLC/R_f = 0.16 (Cyclohexane/EtOAc 4/6); mp 231–232 °C; Yield: 52%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.77 (s, 2H, NC*H*$_2$CO), 7.08 (d, 1H, *J* = 8.1 Hz, Ph*H*), 7.31 (t, 1H, *J* = 7.8 Hz, Ph*H*), 7.46 (dd, 1H, *J* = 8.0 Hz, *J* = 4.7 Hz, Ar*H*), 7.56 (td, 1H, *J* = 8.1 Hz, *J* = 1.4 Hz, Ph*H*), 7.98 (dd, 1H, *J* = 7.8 Hz, *J* = 1.4 Hz, Ph*H*), 8.33 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, Ar*H*), 8.51 (br, 1H, N*H*), 8.75 (dd, 1H, *J* = 4.7 Hz, *J* = 1.5 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 49.7 (CH_2CO), 120.6, 122.1, 124.6, 124.8, 131.9, 133.0, 133.1, 135.9, 141.7 (CNO_2), 145.3, 151.8, 166.7 (CO), 169.1 (CO); HRMS: *m/z* (APCI) 299.0780 (MH^+ $C_{14}H_{10}N_4O_4H^+$ requires 299.0780).
12. *General procedure for the formation of imidazo[4,5-b]pyridine derivatives* (**4a–j**): NH_4Cl (1.27 mmol, 0.6 equiv) and iron (6.36 mmol, 3 equiv) were added to a stirring solution of the 3-nitropyridine derivatives (**2a–i** and **6**) (2.12 mmol, 1 equiv) in EtOH/H_2O (2 mL/2 mL). The mixture was stirred at 80 °C (2 h). The mixture was filtered through a pad of Celite. The pad was washed with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and the solvents were evaporated under vacuum. The residue was solubilized in CH_2Cl_2 (5 mL) and the solution was introduced into a μ-wave tube and then triethylamine was added (8.48 mmol, 4 equiv) followed by $SiCl_4$ (5.30 mmol, 2.5 equiv). The solution was microwave heated at 110 °C (15 min) with stirring. The reaction was quenched by addition of an aqueous saturated solution of $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc) to obtain the imidazo[4,5-*b*]pyridine derivatives. 6-Methoxy-dipyrido[1,2-*a*;3′,2′-*d*]imidazole (**4h**); white solid; TLC/R_f = 0.47 (EtOAc); Yield: 65%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.11 (s, 3H, OC*H*$_3$), 6.78 (d, 1H, *J* = 6.9 Hz, Ph*H*), 7.49 (t, 1H, *J* = 6.9 Hz, Ph*H*), 7.51 (dd, 1H, *J* = 8.3 Hz, *J* = 4.5 Hz, Ar*H*), 8.25 (dd, 1H, *J* = 8.3 Hz, *J* = 1.3 Hz, Ar*H*), 8.46 (d, 1H, *J* = 6.9 Hz, Ph*H*), 8.51 (d, 1H, *J* = 4.5 Hz, Ar*H*); Dept-135 ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 56.0 (CH_3), 105.9, 111.0, 116.8, 121.5, 127.7, 142.6; LRMS: *m/z* (APCI) 200.0 (MH^+. $C_{11}H_{10}N_3O$ requires 200.0). 5-Methyl-5H-5,7a,8,12-tetraaza-dibenzo[*a,e*]azulen-6-one (**4i**); brown solid; TLC/R_f = 0.17 (EtOAc); Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.41–3.46 (m, 4H, NMe and C*H*H′N), 3.49 (d, 1H, *J* = 6.7 Hz, CH*H*′N), 7.33 (dd, 1H, *J* = 8.2 Hz, *J* = 4.8 Hz, Ar*H*), 7.47 (m, 2H, Ph*H*), 7.66 (td, 1H, *J* = 7.8 Hz, *J* = 1.6 Hz, Ph*H*), 8.16 (m, 2H, Ar*H* and Ph*H*), 8,45 (dd, 1H, *J* = 4.8 Hz, *J* = 1.4 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 37.1 (CH_3), 44.1 (CH_2), 118.9, 122.9, 126.2, 127.4, 130.3, 131.7, 134.9, 140.1, 144.2, 159.8 (C imid), 165.9 (CO); LRMS: *m/z* (APCI) 265.0 (MH^+. $C_{15}H_{12}N_4OH^+$ requires 265.29).
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