Directed Deprotonation-Transmetallation of 4-Bromopyridine: Flexible Routes to Substituted Pyridines

Gunter Karig,[a] Nopporn Thasana,[a,b,c] Timothy Gallagher*[a]

[a] School of Chemistry, University of Bristol, Bristol BS8 1TS, UK
Fax +44(117)9298611; E-mail: T.Gallagher@bristol.ac.uk

[b] Chulabhorn Research Institute, Bangkok 10210, Thailand

[c] Department of Chemistry, Mahidol University, Bangkok 10400, Thailand

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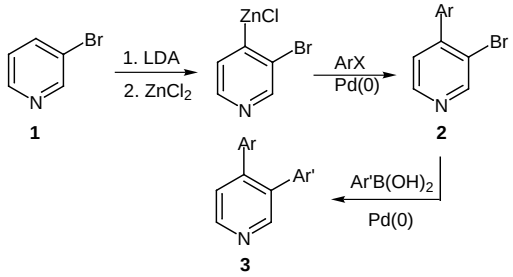
Abstract: Halide-directed deprotonation and Li-Zn exchange of 4-bromopyridine **4** provides organozinc **6,** which undergoes Pd-mediated coupling to give the 3-aryl-4-bromopyridines **7**. Further substitution is achieved to provide the 3,4-disubstituted pyridines **8** and **9**, and the 3,4,5-trisubstituted variants **10**.

Key words: directed lithiation, transmetallation, cross-coupling, zinc, pyridine

We[1] recently described an entry to ring substituted pyridines based on a sequence involving (i) the halide-directed deprotonation (ii) transmetallation to generate a pyridyl organozinc and (iii) Pd(0)-mediated Negishi cross coupling.[2,3] This methodology is illustrated in Scheme 1 for 3-bromopyridine **1**, which leads to 3, 4-disubstituted pyridines such as **2** and **3**. Similar methodology applied to 2-bromopyridine provides access to 2,3- and also 2,4-disubstituted heteroarenes.[1]



Scheme 1

In this paper we describe the application of this directed deprotonation, transmetallation, cross coupling sequence to 4-bromopyridine **4**.[4] This is significant because this substrate complements 3-bromopyridine in terms of the substitution and reactivity profiles that are available. In addition, we have found that **4** undergoes sequential substitution at *C*(*3*) and then *C*(*5*) to provide 3,4,5-trisubstituted pyridines. These transformations are illustrated, together with the products obtained, in Schemes 2 and 3. It is also pertinent to recognize the issues associated with use of 4-bromopyridine. This reactant is commercially available as the hydrochloride salt, but the free base is unstable and (unlike 2- or 3-bromopyridine) is prone to rapid polymerization.

Deprotonation of 4-bromopyridine **4** (HCl salt) was carried out using LDA (2.2 equiv) in THF essentially as described by Gribble,[4] except that we conducted this step at –78 °C rather than use lower temperatures (–90 °C, Scheme 2). $ZnCl_2$ (in THF) was added and the resulting mixture was allowed to warm to room temperature. While the organolithium intermediate **5** is prone to decomposition, the corresponding organozinc derivative **6** appears to be stable at room temperature if kept under an inert atmosphere. Exposure of **6** to an aryl iodide in the presence of $Pd(PPh_3)_4$ (10 mol%) gave the 3-aryl-4-bromopyridines **7a**–**d** in 34–53% yield.[5,6] These yields, which are based on the aryl iodide, are significantly lower than the corresponding reactions involving 2-bromopyridine or 3-bromopyridine, and likely reflect the instability associated with the 4-bromo substituent of both **4** and **7**. By-products from these processes, though not fully characterized, did incorporate diisopropylamine. A more hindered base should suppress such side reactions, and it is interesting to note that use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP)[7] gave **7c** in 46% yield (compared to 34% with LDA).

Furthermore, the 4-bromopyridines **7** are capable of undergoing both Suzuki cross couplings[8] and Heck reactions to provide the 3,4-diarylpyridines **8a**–**c** and 3-aryl-4-alkenylpyridines **9a** and **9b**.

The role of the *C*(*4*) bromo substituent in **4** is to assist and direct deprotonation at *C*(*3*). With substitution to give **7** complete, the *C*(*5*) proton remains available for activation and substitution, providing a vehicle for 3,5-diarylation. This has been achieved, and exposure of **7d** to LDA at –78 °C, followed by $ZnCl_2$ (–78 °C to r.t.) and Pd(0)-mediated coupling with either 1-iodo-4-nitrobenzene or iodobenzene gave 4-bromo-3-(4-nitrophenyl)-5-phenylpyridine **10a** and 4-bromo-3,5-diphenylpyridine **10b** in 34% and 44% yields respectively (Scheme 3).[9,10]

In summary, we have extended the scope of the directed deprotonation-transmetallation of bromopyridines to include 4-bromopyridine **4**. The instability of the 4-bromo moiety is a complication that does not apply to the other bromopyridines, nevertheless the 3-pyridyl zinc intermediate **6** is available and undergoes Negishi coupling to

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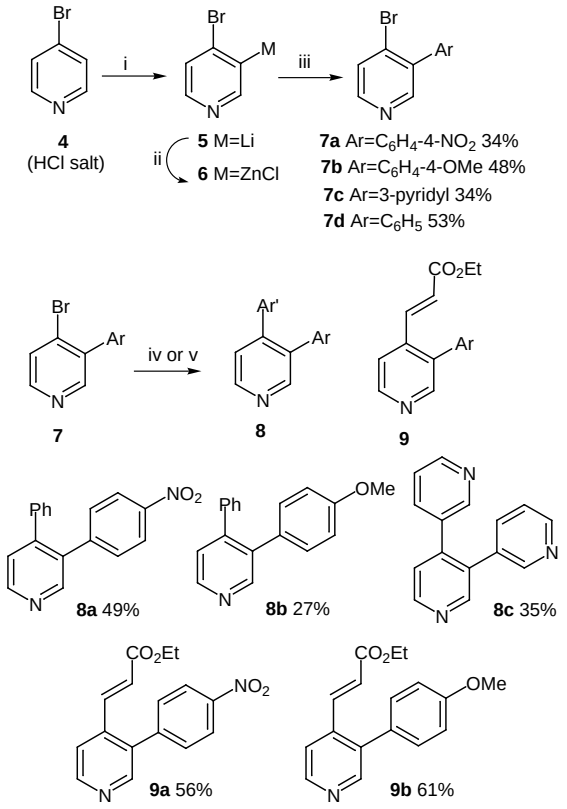
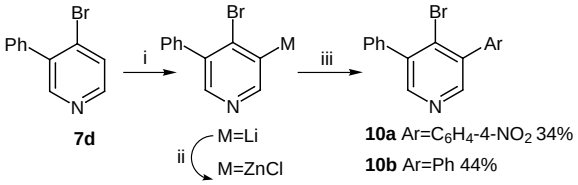


Scheme 2 *Reagents*: i, LDA (2.2. equiv), THF, –78 °C; ii, $ZnCl_2$ (in THF), –78 °C to r.t.; iii, ArX (X = I or Br), $Pd(PPh_3)_4$, THF, reflux; iv, Suzuki: Ar′$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, EtOH, reflux; v, Heck: CH_2=$CHCO_2Et$, $Pd(OAc)_2$, NEt_3, P(*o*-Tol)$_3$, MeCN, reflux.



Scheme 3 *Reagents*: i, LDA (1.1 equiv), THF, –78 °C; ii, $ZnCl_2$ (in THF), –78 °C to r.t.; iii, ArI (see text), $Pd(PPh_3)_4$, THF, reflux.

give a range of 3,4-disubstituted derivatives, complementing the regiochemistry available for 3-bromopyridine (compare **3** and **8**). Furthermore, substitution at both *C*(*3*) and *C*(*5*) can be accomplished in a stepwise manner leading to more highly substituted pyridines, such as **10**.

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(5) All new compounds have been fully characterized by IR, ^1H and ^{13}C NMR, and HRMS. Selected data are presented below. It is noteworthy that the bromo moiety of **6** does not participate in a 'homocoupling' process [i.e. a Pd(0)-mediated dimerization of **6**], and only the cross coupled product **7** is observed. Furthermore, in addition to aryl iodides, organozinc **6** has also been coupled successfully to vinyl triflates.

(6) We used an excess (2.5 equiv as compared to the aryl iodide) of 4-bromopyridine and yields are based on the aryl iodide component. A solution of LDA [from diisopropylamine (1.4 mL, 10 mmol), *n*-BuLi (4 mL, 2.5 M in hexanes, 10 mmol) in THF (5 mL)] was transferred to a solution of 4-bromopyridine hydrochloride (970 mg, 5 mmol) in THF (5 mL) at –78 °C and stirred for 30 min. Dry $ZnCl_2$ (700 mg, 5 mmol) in THF (5 mL) was added. A precipitate was formed and the mixture was allowed to warm to room temperature. Aryl iodide (2 mmol) and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) were added and the reaction mixture was heated to reflux for 3 hours. After cooling, sat. aq NH_4Cl was added, and the product was extracted with EtOAc, the extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Purification by silica gel flash chromato-graphy gave the 3-aryl-4-bromopyridines **7**.
Selected data for 3-aryl-4-bromopyridines: **7a**: mp 169 °C (EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2 H, d, *J* = 8.8 Hz, C*H*2′,6′), 7.68 (1 H, d, *J* = 5.3 Hz, C*H*5), 8.36 (2 H, d, *J* = 8.9 Hz, C*H*3′,5′), 8.46 (1 H, d, *J* = 5.3 Hz, C*H*6), 8.53 (1 H, s, C*H*2). **7b**: mp 60-62 °C (EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (3 H, s, OCH_3), 7.01 (2 H, d, *J* = 8.8 Hz, C*H*3′,5′), 7.37 (2 H, d, *J* = 8.8 Hz, C*H*2′,6′), 7.61 (1 H, dd, *J* = 0.4, 5.3 Hz, C*H*5), 8.33 (1 H, d, *J* = 5.3 Hz, C*H*6), 8.50 (1 H, s, C*H*2). **7c**: mp 69–70 °C (EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1 H, dd, *J* = 5.1, 7.9, Hz, C*H*5′), 7.67 (1 H, d, *J* = 5.3 Hz, C*H*5), 7.79 (1 H, d, *J* = 7.9 Hz, C*H*4′), 8.44 (1 H, d, *J* = 5.2 Hz, C*H*6), 8.53 (1 H, s, C*H*2), 8.70 (2 H, s, C*H*2′,6′). **7d**: oil ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (5 H, m, Ph*H*), 7.61 (1 H, dd, *J* = 0.5, 5.3 Hz, C*H*5), 8.33 (1 H, d, *J* = 5.3 Hz, C*H*6), 8.51 (1 H, s, C*H*2).

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(8) General procedure for Suzuki coupling of **7** to give **8**: To the 4-bromo-3-arylpyridines **7** (0.2 mmol) in toluene (9 mL) and EtOH (1 mL) were added aryl boronic acid (0.25 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.017 mmol) and 10% aq Na_2CO_3 (3 mL). The mixture was heated at reflux for 3 hours, then cooled, filtered, and extracted with EtOAc. The extracts were washed with water, dried ($MgSO_4$), concentrated and the product was isolated following flash chromatography. Selected data for 3,4-diarylbromopyridines: **8a** mp 124–125 °C (EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (2 H, m, C*H*3′′,5′′), 7.31 (3 H, m, C*H*2′′,4′′,6′′), 7.33 (2 H, d, *J* = 8.9 Hz, C*H*2′,6′), 7.40 (1 H, d, *J* = 4.9 Hz, C*H*5), 8.15 (2 H, d, *J* = 8.9 Hz, C*H*3′,5′), 8.66 (1 H, s, C*H*2); 8.71 (1 H, br.d, *J* = 4.0 Hz, C*H*6). **8b** mp 110–111 °C (EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (3 H, s, OCH_3), 6.81 (2 H, d, *J* = 8.6 Hz, C*H*3′,5′), 7.07 (2 H, d, *J* = 8.6 Hz, C*H*2′,6′), 7.17 (2 H, m, C*H*3′′,5′′), 7.28 (3 H, m, C*H*2′′,4′′,6′′), 7.33 (1 H, d, *J* = 5.1 Hz, C*H*5), 8.60 (1 H, br.d, C*H*6); 8.62 (1 H, br.s, C*H*2). **8c** mp 133–134 °C (EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.25 (2 H, m, C*H*5′,5′′), 7.41 (1 H, dd, *J* = 0.7, 4.6 Hz, C*H*5), 7.44 (2 H, m, C*H*4′,4′′), 8.46 (2 H, m, C*H*2′,2′′), 8.57 (2 H, m, C*H*6′,6′′), 8.70 (1 H, br.s, C*H*2); 8.75 (1 H, d, *J* = 4.6 Hz, C*H*6).

(9) A solution of LDA [from diisopropylamine (0.35 mL, 2 mmol), *n*-BuLi (1 mL, 2.0 M in hexanes, 2 mmol) in THF (2 mL)] was transferred to a solution of **7d** (250 mg, 1 mmol) in THF (2 mL) at –78 °C and stirred for 30 min. $ZnCl_2$ (138 mg, 1 mmol) in THF (2 mL) was added. A precipitate was formed and the mixture was allowed to warm to room temperature. 1-Iodo-4-nitrobenzene (or iodobenzene) (1 mmol) and $Pd(PPh_3)_4$ (0.015 g, 0.01 mmol) were added and the reaction mixture was heated at reflux for 3 hours. After cooling, saturated aqueous NH_4Cl was added, and the product was extracted with EtOAc, the extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Purification by silica gel flash chromatography gave the 3,5-diaryl-4-bromopyridines **10**.
Selected data for 3,5-diaryl-4-bromopyridines: **10a** mp 153–154 °C (EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (5 H, m, Ph*H*), 7.53 (2 H, d, *J* = 9.0 Hz, C*H*3′,5′), 8.36 (2 H, d, *J* = 9.0 Hz, C*H*2′,6′), 8.45 (1 H, s, C*H*2); 8.53 (1 H, s, C*H*6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.6 (*C*H), 128.4 (*C*H), 128.6 (*C*H), 129.5 (*C*H), 130.8 (*C*H), 133.0 (*C*), 137.2 (*C*), 137.3 (*C*), 139.4 (*C*), 144.3 (*C*), 147.8 (*C*),148.8 (*C*H), 150.5 (*C*H). **10b** mp 116–117 °C (EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (10 H, m, Ph*H*), 8.45 (2 H, s, C*H*2, 6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.3 (*C*H), 128.4 (*C*H), 129.6 (*C*H), 133.4 (*C*), 137.9 (*C*), 139.1 (*C*), 149.4 (*C*H).

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