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A convenient one-pot Negishi coupling of amino-heteroaryl chlorides and alkyl bromides

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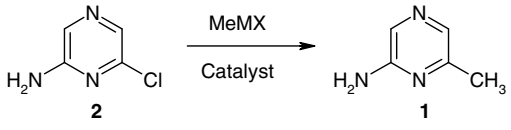
Abstract—A simple Ni-catalysed cross-coupling protocol for amino-heteroaryl chlorides with alkylzinc reagents has been developed. The alkylzinc reagents can be commercially available dialkylzincs or alkylzinc halides, or can be conveniently generated in situ from diethylzinc and primary alkyl bromides in the presence of the same inexpensive Ni catalyst used to effect the subsequent coupling reaction.

We recently sought a convenient synthesis of alkylaminoheterocycles such as 6-methyl-2-aminopyrazine **1** for a drug discovery programme. Although there are several syntheses of **1** reported in the literature, they are all multi-step procedures or produce mixtures of isomers.[1] The commercial availability of 2-amino-6-chloropyrazine **2** encouraged us to develop a direct single step transition metal-mediated methylation of this material (Scheme 1).

The Negishi Ni or Pd mediated cross-coupling reaction[2] of organozinc reagents and aryl or alkyl halides is well known to tolerate a range of functionality.[3] Indeed, there are many examples of Negishi reactions on haloanilines.[4] However, there are few cases involving heteroaryl halides as the electrophile, all of which employ arylzinc reagents as coupling partners.[5] The Ni-catalysed Negishi coupling of dimethylzinc with alkyl-substituted chloropyrazines is known,[6] so these conditions seemed worth investigating for the methylation of **2**.



Scheme 1.

Direct application of these literature conditions to **2** (1.2 equiv of dimethylzinc and 5 mol % [1,3-bis(diphenylphosphino)propane]nickel(II) chloride in refluxing THF) failed to afford any of the desired methylation product **1**. However, doubling the quantity of dimethylzinc and switching to refluxing dioxane as solvent gratifyingly afforded **1** in reasonable yield (Table 1, entry 1). The reaction proved readily amenable to scale up, with the same yield obtained whether on a 1 mmol or 0.1 mol scale.

With the objective of a simple one-step synthesis of **1** in hand, it was of interest to explore the generality of this process. The same conditions[7] proved equally successful with diethylzinc, affording 6-ethyl-2-aminopyrazine **3** in good yield (Table 1, entry 2). At this point, the limited commercial availability of diorganozincs proved restrictive, so it was pleasing to observe that the Negishi coupling reaction proceeded equally well with 4 equiv of methylzinc chloride (Table 1, entry 3). A wide variety of alkylzinc halides are commercially available, and both propyl and cyclopentylzinc halides were found to couple effectively to aminopyrazine **2** (Table 1, entries 4 and 5), suggesting that this procedure may be reasonably general for alkylzinc halides.

It has been shown by Knochel and co-workers that Ni catalysis is capable of effecting the halogen–zinc exchange of primary alkyl halides with excess diethylzinc.[9] This

Keywords: Negishi coupling; Nickel; Halogen–zinc exchange; Alkylaminopyrazine.
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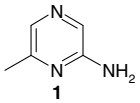
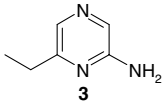
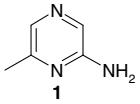
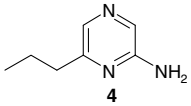
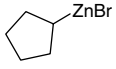
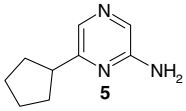
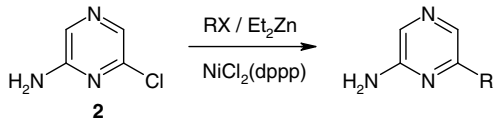
Table 1. Negishi couplings of 2-amino-6-chloropyrazine **2** with organozinc reagents

Entry	Reagents[a]	Time (h)	Product	Yield[b] (%)
1	Me_2Zn (2 equiv)	24	 **1**	50
2	Et_2Zn (2 equiv)	5	 **3**	89
3	MeZnCl (2 equiv) MeZnCl (4 equiv)	24 5	 **1**	20 60
4	PrZnCl (4 equiv)	2	 **4**	92
5	 (4 equiv)	2	 **5**	46

[a] All reactions performed in refluxing dioxane with 10 mol % $NiCl_2$(dppp).
[b] Yields of products isolated after column chromatography.[8]

raised the interesting prospect of using the same Ni catalyst to both form the alkylzinc halide in situ and also bring about its coupling to the chloropyrazine **2** in a one-pot procedure (Scheme 2).



Scheme 2.

It was found that halogen–zinc exchange could be brought about using an excess of alkyl halide and a 1 M solution of diethylzinc. This allowed the direct addition of the heteroaryl chloride for Negishi coupling without any intermediate manipulations such as evaporation of excess diethylzinc. Thus treatment of diethylzinc with a 20% excess of phenethyl iodide in the

Table 2. One-pot halogen–zinc exchange/Negishi coupling reactions

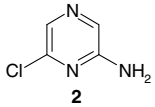
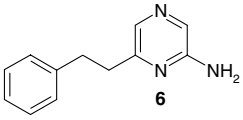
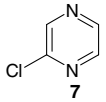
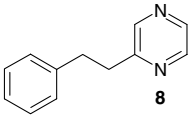
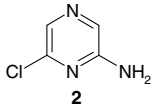
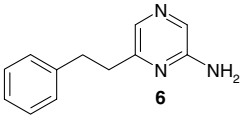
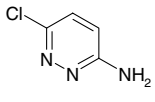
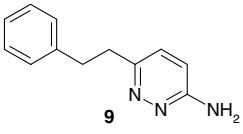
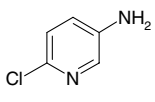
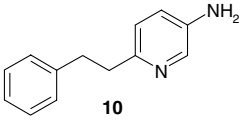
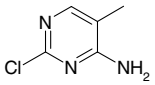
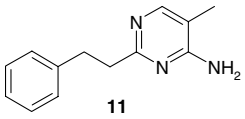
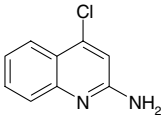
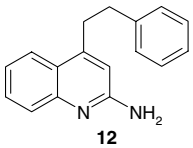
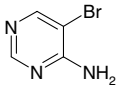
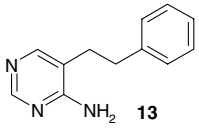
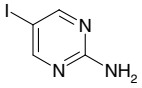
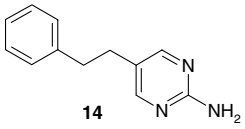
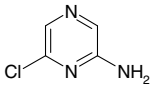
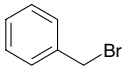
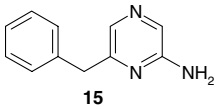
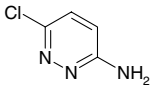
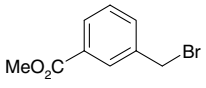
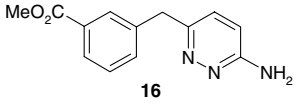
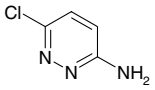
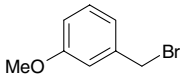
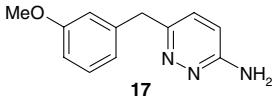
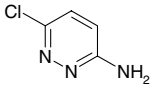
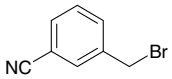
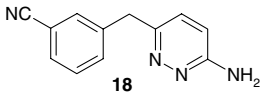
Entry	Amino-heteroaryl halide	Alkyl halide[a]	Product	Yield[b] (%)
1	 **2**	$Ph(CH_2)_2I$	 **6**	43
2[c]	 **7**	$Ph(CH_2)_2Br$	 **8**	42
3	 **2**	$Ph(CH_2)_2Br$	 **6**	43
4		$Ph(CH_2)_2Br$	 **9**	60
5		$Ph(CH_2)_2Br$	 **10**	45

Table 2 (*continued*)

Entry	Amino-heteroaryl halide	Alkyl halide[a]	Product	Yield[b] (%)
6		$Ph(CH_2)_2Br$	 **11**	37
7		$Ph(CH_2)_2Br$	 **12**	69
8		$Ph(CH_2)_2Br$	 **13**	52
9		$Ph(CH_2)_2Br$	 **14**	13
10[d]	 **2**		 **15**	50
11[d]			 **16**	69
12[d]			 **17**	40
13[d]			 **18**	63

[a] Standard conditions: alkyl halide (6 mmol), diethylzinc (5 mmol) and $NiCl_2$(dppp) (0.2 mmol) heated at 65 °C for 4 h in dioxane, amino-heteroaryl halide (1 mmol) added and refluxed for 2 h.
[b] Yields of products isolated after column chromatography.[8]
[c] Standard conditions except alkyl halide (5 mmol), diethylzinc (3.5 mmol).
[d] Standard conditions except alkyl halide, diethylzinc and $NiCl_2$(dppp) heated at 100 °C for 4 h before addition of amino-heteroaryl halide (0.5 mmol).

presence of 20 mol % $NiCl_2$(dppp) at 65 °C in dioxane for 3 h brought about an efficient iodine–zinc exchange. This was shown by subsequent addition of chloropyrazine **2** followed by refluxing for 8 h, which afforded the cross-coupled product **6** in moderate yield with less than 10% of the ethyl product **3** observed (Table 2, entry 1). Once again, several equivalents of organozinc reagent were required for effective cross-coupling (a feature also apparent in the Negishi reactions of 2-amino-6-iodopurines in Ref. 5d). Presumably the excess zinc reagent is required due to coordination of the nitrogen atoms of the halide substrates with the active zinc species. Even when the amino group was removed from the heteroaryl halide substrate, 3.5 equiv of diethylzinc were still required to achieve comparable yields of the cross-coupling product **8** from chloropyrazine **7** (Table 2, entry 2). The halogen–zinc exchange was also found to proceed equally well with primary alkyl bromides (Table 2, entries 2 and 3), although it failed with phenethyl chloride.

Further attempts to generalise this reaction met with some success.[10] Using phenethyl bromide as a model alkyl halide, the one-pot halogen–zinc exchange/Negishi coupling reaction proved to be effective with a range of different amino-heteroaryl chlorides (Table 2, entries

4–7). The reaction also worked with an amino-heteroaryl bromide (Table 2, entry 8), but afforded poor yields with an iodide (Table 2, entry 9), and gave no product at all with 3-chloro- or 3-iodoaniline or 4-chloro-2-aminothiazole. The reaction conditions are tolerant of several useful functional groups in the alkyl halide coupling partner (Table 2, entries 11–13).

In conclusion, a practical Ni-catalysed one-pot coupling of amino-heteroaryl chlorides and alkylzinc reagents has been demonstrated. The alkylzinc reagents can be commercially available dialkylzincs or alkylzinc halides, or can be conveniently generated in situ from diethylzinc and primary alkyl bromides in the presence of the same inexpensive Ni catalyst used to effect the subsequent coupling reaction.

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7. General procedure: A 1 M THF or toluene solution of the organozinc reagent (2 mmol if diorganozinc or 4 mmol if alkylzinc halide) was added to a solution of 6-chloro-2-aminopyrazine (1 mmol) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (0.1 mmol) in dry dioxane (5 mL) under an atmosphere of nitrogen. The reaction mixture was heated at reflux for the length of time indicated in Table 1. The reaction was quenched with methanol and concentrated in vacuo. The residue was partitioned between ethyl acetate and brine, and the organic phase dried over magnesium sulfate, filtered and evaporated. The crude product was purified by silica gel chromatography, eluting with dichloromethane/methanol, to afford the alkyl-aminopyrazines in >95% purity.
8. All compounds described herein have been fully characterised by ^{1}H and ^{13}C NMR spectroscopy, mp, MS, and elemental analysis or accurate mass MS. For example: *2-Amino-6-propylpyrazine* **4**: mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81 (1H, s), 7.79 (1H, s), 4.47 (2H, br s), 2.58 (2H, t, $J = 7.5$ Hz), 1.78–1.65 (2H, m), 0.97 (3H, t, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): 154.88, 153.75, 133.50, 129.47, 37.21, 22.56, 13.79; HRMS calcd for $C_7H_{11}N_3$: 138.1031 $[M+H]^+$, found 138.1029 $[M+H]^+$. *2-Amino-6-cyclopentylpyrazine* **5**: mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (1H, s), 7.78 (1H, s), 4.45 (2H, br s), 3.07–2.96 (1H, m), 2.04–1.95 (2H, m), 1.84–1.64 (6H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 158.41, 153.78, 132.69, 129.33, 44.96, 33.00, 25.76; HRMS calcd for $C_9H_{13}N_3$: 164.1187 $[M+H]^+$, found 164.1187 $[M+H]^+$. *2-Amino-6-(2-phenylethyl)pyrazine* **6**: mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.80 (2H, br s), 7.31–7.16 (5H, m), 4.50 (2H, br s), 3.04–2.89 (4H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 153.86, 141.20, 133.44, 129.76, 128.40, 128.38, 126.06, 36.95, 35.34; HRMS calcd for $C_{12}H_{13}N_3$: 200.1187 $[M+H]^+$, found 200.1194 $[M+H]^+$. *4-Amino-5-methyl-2-(2-phenylethyl)pyrimidine* **11**: mp 126–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (1H, s), 7.30–7.16 (5H, m), 4.80 (2H, br s), 3.12–2.99 (4H, m), 2.06 (3H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 168.07, 161.75, 155.22, 141.81, 128.41, 128.29, 125.80, 110.14, 40.78, 34.71, 13.39. Anal. Found: C, 73.00; H, 6.99; N, 19.90. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. *2-Amino-4-(2-phenylethyl)quinoline* **12**: mp 156–159 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (1H, d, $J = 8.2$ Hz), 7.70 (1H, d, $J = 8.5$ Hz), 7.57 (1H, t, $J = 8.2$ Hz), 7.34–7.21 (6H, m), 6.52 (1H, s), 4.74 (2H, br s), 3.28–3.24 (2H, m), 3.06–3.02 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 156.74, 149.00, 148.09, 141.13, 129.41, 128.50, 128.35, 126.80, 126.25, 123.18, 122.96, 122.55, 110.91, 35.83, 34.07. Anal. Found: C, 82.06; H, 6.49; N, 11.33. Calcd for $C_{17}H_{16}N_2$: C, 82.23; H, 6.49; N, 11.28. *3-[(6-amino-3-pyridazinyl)methyl]-benzoic acid methyl ester* **16**: mp 214–216 °C; ^{1}H NMR($CDCl_3$, 300 MHz): δ 7.94 (1H, s), 7.91 (1H, d, $J = 7.6$ Hz), 7.46 (1H, d, $J = 7.6$ Hz), 7.37 (1H, t, $J = 7.6$ Hz), 7.02 (1H, d, $J = 9.1$ Hz), 6.67 (1H, d, $J = 9.1$ Hz), 4.67 (2H, br s), 4.24 (2H, s), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 166.16, 159.44, 152.35, 140.65, 133.66, 129.77, 129.23, 128.91, 127.90, 127.06, 114.53, 52.09, 40.39. Anal. Found: C, 64.00; H, 5.47; N, 17.00. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27.
9. Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473–7481.
10. General procedure: Diethylzinc (5 mmol of a 1.1 M solution in toluene) was added to a solution of [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (0.2 mmol) in dry dioxane (5 mL) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 10 min before addition of the alkyl halide (6 mmol). Stirring was continued at 65 °C for 4 h, then the amino-heteroaryl halide (1 mmol) was added as a solid (or solution in 2 mL dioxane if soluble) and the reaction mixture heated at reflux for 2 h. The reaction was quenched with methanol and concentrated in vacuo. The residue was diluted with methanol (3 mL) and concentrated hydrochloric acid (3 mL) was added. The mixture was then basified with concentrated ammonia and partitioned between ethyl acetate and brine. The organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by silica gel chromatography, eluting with dichloromethane/methanol, to afford the alkyl aminoheterocycles in >95% purity.