

Some regioselective cross-coupling reactions of halopyridines and halopyrimidines

Nadja M. Simkovsky,^{*a} Monika Ermann,^a Stanley M. Roberts,^a David M. Parry^b and Andy D. Baxter^b

^a Department of Chemistry, University of Liverpool, PO Box 147, Liverpool, UK L69 3BX

^b Celltech R&D Ltd, Granta Park, Cambridge, UK CB1 6GS

Received (in Cambridge, UK) 23rd May 2002, Accepted 19th July 2002

First published as an Advance Article on the web 29th July 2002

An efficient procedure for cross-coupling of 3-bromopyridine and 4-bromoanisole to various mono- and dichloro heteroaryl compounds—giving the corresponding biaryls in 74–96% yield—is described.

Introduction

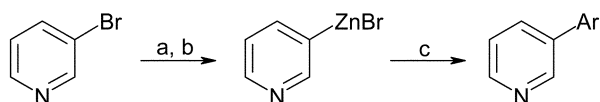
The bipyridine group is a key feature in some important natural products, such as the caerulomycins and collismycins which show antibiotic and cytotoxic activities.^{1,2} Similarly selected pyridylpyrimidines display biological activity; some have potential use as fungicides, acting by cycling copper through the cell membrane where it accumulates internally to toxic levels.³ Furthermore, pyridylpyrimidine scaffolds have been identified as tyrosine kinase inhibitors.^{4–6}

Nowadays bipyridines are frequently synthesised by transition metal catalysed cross-coupling reactions,^{1,7–9} while in contrast substituted pyrimidines such as pyridylpyrimidines are often prepared *via* the classical route by construction of a pyrimidine ring from the appropriate guanidine derivative.^{4,10–12}

Herein we report a high yielding protocol for the preparation of bipyridines, pyridylpyrimidines, and pyridylquinolines with excellent regio-control employing palladium-catalysed cross-coupling reactions.

Results and discussion

As an approach to heteroaryl pyridines cross-coupling under Negishi conditions was studied, which involves the reaction of a pyridylzinc halide with a suitable coupling partner (Scheme 1).



Scheme 1 Representation of the Negishi reaction for the cross-coupling of 3-pyridylzinc bromide with a heteroaryl species (Ar–H). *Reagents and conditions:* a) BuLi, diethyl ether, $-78\text{ }^{\circ}\text{C}$ b) ZnBr₂, diethyl ether, $-78\text{ }^{\circ}\text{C}$ to rt, c) Ar–Cl, THF, Pd(PPh₃)₄, reflux.

Pyridylzinc halides have been previously prepared by the oxidative addition of active zinc to pyridyl halides.^{13,14} Alternatively, they can be prepared *via* metal–metal exchange of lithiopyridines.¹⁵

Our studies focused on the latter method thus avoiding the need to prepare and handle active zinc.

The initial lithiation of a heterocycle is the key step in this cross-coupling process. Such a lithiation requires low temperature; the reaction of bromopyridines has to be performed at $-100\text{ }^{\circ}\text{C}$ in THF or around $-40\text{ }^{\circ}\text{C}$ in diethyl ether, in order to avoid side-reactions such as deprotonation, elimination to give pyridynes, bromine migration, or ring opening reactions.^{16–18}

Attempts to lithiate 3-bromopyridine with *n*-BuLi in THF at $-100\text{ }^{\circ}\text{C}$ did not give satisfactory results. After addition of zinc bromide to 3-lithiopyridine a gummy residue was obtained.

Lithiation and metal–metal exchange were better carried out in ether at $-78\text{ }^{\circ}\text{C}$, with solvent exchange such that the cross-coupling was performed in THF. Pleasingly an excellent yield was achieved on using an excess of bromopyridine, butyllithium and zinc bromide to give 4-pyridyl-2-chloropyrimidine (Table 1, entry 1). Care was taken not to use too large an excess of reagents as over-reaction could occur, involving the second chlorine atom, giving rise to substantial amounts of dipyridylpyrimidine. The method was then extended to other dichloro heterocycles, namely 2,3- and 2,5-dichloropyridines and 4,7-dichloroquinoline as well as 2-chloropyridine and 2-chloropyrimidine (Table 1, entries 2–6). In all cases highly satisfactory yields of a single product were obtained; in cases 1–4 regioselective coupling was observed.

To show the scope of the reaction we have extended the methodology to bromoanisole, which (in contrast to 3-bromopyridine) can be lithiated in THF at $-78\text{ }^{\circ}\text{C}$ (Table 2). Once again clean, high-yielding reactions were observed.

Conclusions

By judicious choice of experimental conditions excellent coupling reactions involving two heterocyclic species can be achieved extending the range of products previously reported by other groups.³

Experimental

2-(3'-Pyridyl)-5-chloropyridine

3-Bromopyridine (1.42 eq., 3.06 mmol) was dissolved in anhydrous diethyl ether (2 mL mmol⁻¹) under a nitrogen atmosphere and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (1.49 eq., 1.6 M solution in hexanes, 3.22 mmol) was then introduced dropwise and the resulting bright yellow mixture stirred for a further 25 minutes. ZnBr₂ (1.49 eq., 3.22 mmol) was dried under vacuum for at least 1 hour and then stirred with anhydrous diethyl ether (3.5 mL mmol⁻¹) until fully dissolved. The zinc bromide solution was added quickly to the lithiated species and stirred for 50 minutes at $-78\text{ }^{\circ}\text{C}$; the cooling bath was removed and the mixture allowed to warm to rt under vacuum. The residue was dissolved in anhydrous THF (5 mL mmol⁻¹ 3-bromopyridine), 2,5-dichloropyridine (1 eq., 2.16 mmol) was added followed by tetrakis(triphenylphosphine)palladium (0.047 eq., 0.10 mmol) and the light yellow solution heated to reflux for 18 hours. Ethyl acetate was added (10 mL) and the basic components dissolved into the aqueous layer with 2 M HCl solution (4 × 10 mL). The pH was re-adjusted to about 10 with solid NaOH and the mixture extracted with ethyl acetate (4 × 15–20 mL). The organic layer was washed with water (2 × 30 mL), dried over MgSO₄, filtered and evaporated. The crude product was further purified by flash column chromatography (petroleum ether (PE) : EtOAc 1 : 2) to obtain the title compound (348 mg, 87%).

Mp 68–69 °C; *R*_f (PE : EtOAc 1 : 2) 0.22; $\nu_{\text{max}}/\text{cm}^{-1}$ 3034, 1582, 1470, 1416, 1367, 1118, 1009, 868, 749, 703, 620; δ_{H} (300 MHz, CDCl₃) 7.40 (1H, ddd, *J*_{5,4} 8.1 Hz, *J*_{5,6} 4.8 Hz, *J*_{5,2} 0.9 Hz,

Table 1 Cross-coupling of 3-bromopyridine with various mono- and dichloroheteroaryls

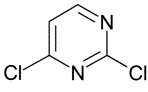
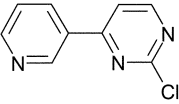
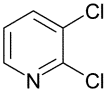
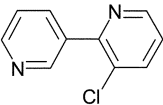
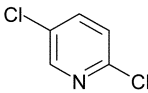
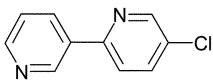
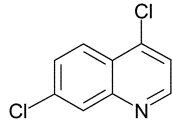
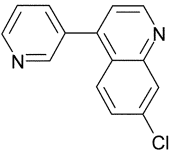

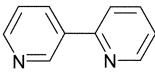

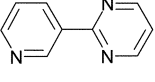
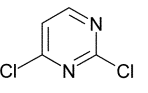
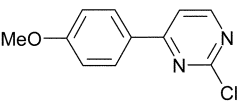

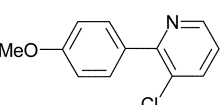
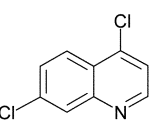
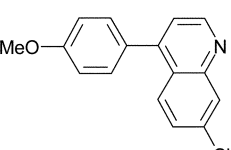

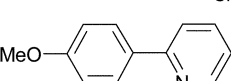

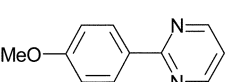
Entry	Substrate	Product	Yield (%)	Ref.
1			88	19
2			74	7
3			87	20
4			75	21
5			90	22
6			89	22

Table 2 Cross-coupling of 4-bromoanisole with various mono- and dichloroheteroaryls

Entry	Substrate	Product	Yield (%)	Ref.
1			90	23
2			88	24
3			78	25
4			82	26
5			96	27

5-H), 7.71 (1H, dd, $J_{3',4'}$ 8.4 Hz, $J_{3',6'}$ 0.9 Hz, 3'-H), 7.78 (1H, dd, $J_{4',3'}$ 8.4 Hz, $J_{4',6'}$ 2.4 Hz, 4'-H), 8.30 (1H, ddd, $J_{4,5}$ 8.1 Hz, $J_{4,2}$ 2.1 Hz, $J_{4,6}$ 2.0 Hz, 4-H), 8.66–8.68 (2H, m, $J_{6,5}$ 4.8 Hz, $J_{6,4'}$ 2.4 Hz, $J_{6,4}$ 1.8 Hz, $J_{6',3'}$ 0.9 Hz, 6-H and 6'-H), 9.18 (1H, dd, $J_{2,4}$ 2.1 Hz, $J_{2,5}$ 0.9 Hz, 2-H); δ_C (75 MHz) 121.1 (d), 123.6 (d), 131.5 (s), 133.8 (s), 134.2 (d), 136.7 (d), 148.1 (d), 149.0 (d), 150.3 (d), 153.0 (d); MS (EI) 192 (33), 191 (33), 190 (100), 189 (79), 164 (25), 155 (13), 76 (13), 74 (10), 51 (16), 50 (26); required C 63.01, H 3.70, N 14.70%; found C 62.94, H 3.73, N 14.78%.

4-(4-Methoxyphenyl)-2-chloropyrimidine

4-Bromoanisole (1.1 eq., 2.59 mmol) was dissolved in anhydrous THF (2 mL mmol⁻¹) under a nitrogen atmosphere and cooled to -78 °C. A solution of BuLi in hexanes (1.2 eq.,

1.52 M solution in hexanes, 2.82 mmol) was added quickly and the resulting mixture stirred for a further 50 minutes. ZnBr₂ (1.3 eq., 3.06 mmol, pre-dried under vacuum for at least 1 hour,) dissolved in anhydrous THF, (2 mL mmol⁻¹) was added quickly and stirring was continued for a further 45 minutes whereupon the cooling bath was removed and the mixture allowed to warm to rt. 2,4-Dichloropyrimidine (1 eq., 2.34 mmol) and tetrakis(triphenylphosphine)palladium (0.047 eq., 0.12 mmol) were added under a flow of nitrogen and the resulting light yellow solution heated to reflux overnight. The mixture was cooled to rt, ethyl acetate was added (20 mL) and the organic layer washed with water (2 × 20 mL), dried over magnesium sulfate, filtered and the solvent evaporated. Purification by column chromatography (PE : EtOAc 2 : 1) gave the title compound (458 mg, 90%)

without any impurities of triphenylphosphine or triphenylphosphine oxide.

Mp 140–141 °C; R_f (PE : EtOAc 2 : 1) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 3064, 2978, 2937, 1610, 1574, 1347, 1258, 1184, 826; δ_{H} (300 MHz, CDCl_3) 3.89 (3H, s, OCH_3), 7.01 (2H, apparent dt, $J_{2,3}$ and $J_{6,5}$ 9.0 Hz, $J_{2,5}$ and $J_{6,3}$ 2.2 Hz, 2-H and 6-H), 7.56 (1H, d, $J_{5',6'}$ 5.4 Hz, 5'-H), 8.08 (2H, apparent dt, $J_{3,2}$ and $J_{5,6}$ 9.0 Hz, $J_{3,6}$ and $J_{5,2}$ 2.2 Hz, 3-H and 5-H), 8.56 (1H, d, $J_{6',5'}$ 5.4 Hz, 6'-H); δ_{C} (75 MHz) 55.4 (q), 114.5 (d), 114.5 (d), 127.5 (s), 129.2 (d), 159.5 (d), 161.8 (s), 162.9 (s), 166.7 (s); MS (EI) 222 (30), 221 (13), 220 (100), 205 (18), 177 (23), 116 (16), 89 (23), 63 (16), 62 (11); required C 59.88, H 4.11, N 12.69, Cl 16.07%; found C 59.68, H 4.08, N 12.59, Cl 16.21%.

References

- 1 F. Trécourt, B. Gervais, M. Mallet and G. Quéguiner, *J. Org. Chem.*, 1996, **61**, 1673.
- 2 F. Trécourt, B. Gervais, O. Mongin, C. Le Gal, F. Mongin and G. Quéguiner, *J. Org. Chem.*, 1998, **63**, 2892.
- 3 S. L. Hargreaves, B. L. Pilkington, S. E. Russell and P. A. Worthington, *Tetrahedron Lett.*, 2000, **41**, 1653.
- 4 J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N. B. Lydon and P. Traxler, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1221.
- 5 B. J. Druker, S. Tamura, E. Buchdunger, S. Ohno, G. M. Segal, S. Fanning, J. Zimmermann and N. B. Lydon, *Nat. Med. (N. Y.)*, 1996, **2**, 561.
- 6 J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer and N. B. Lydon, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 187.
- 7 M. P. Cruskie, J. A. Zoltewicz and K. A. Abboud, *J. Org. Chem.*, 1995, **60**, 7491.
- 8 R. W. Friesen, C. Brideau, C. C. Chan, S. Charleson, D. Deschênes, D. Dubé, D. Ethier, R. Fortin, J. Y. Gauthier, Y. Girard, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, D. Visco, L. J. Xu and R. N. Young, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2777.
- 9 S. Gronowitz, P. Björk, J. Malm and A.-B. Hörnfeldt, *J. Organomet. Chem.*, 1993, **460**, 127.
- 10 H. Brederick, F. Effenberger and H. Bosch, *Ber. Dtsch. Chem. Ges.*, 1964, **97**, 3397.
- 11 M. S. S. Palanki, P. E. Erdman, A. M. Manning, A. Ow, L. J. Ransone, C. Spooner, C. Suto and M. Suto, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1645.
- 12 N. Fujiwara, H. Fujita, K. Iwai, A. Kurimoto, S. Murata and H. Kawakami, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1317.
- 13 T. Sakamoto, Y. Kondo, N. Murata and H. Yamanaka, *Tetrahedron Lett.*, 1992, **33**, 5373.
- 14 T. Sakamoto, Y. Kondo, N. Murata and H. Yamanaka, *Tetrahedron*, 1993, **49**, 9713.
- 15 A. S. Bell, D. A. Roberts and K. S. Ruddock, *Synthesis*, 1987, 843.
- 16 F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Quéguiner, *Tetrahedron*, 2000, **56**, 1349.
- 17 F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Quéguiner, *Tetrahedron Lett.*, 1999, **40**, 4339.
- 18 M. Mallet, G. Branger, F. Marsais and G. Quéguiner, *J. Organomet. Chem.*, 1990, **382**, 319.
- 19 Mp 142–143 °C; R_f (PE : EtOAc 1 : 2) 0.23; $\nu_{\max}/\text{cm}^{-1}$ 3053, 2923, 1595, 1569, 1532, 1408, 1198, 1183, 771, 699, 648; δ_{H} (300 MHz, CDCl_3) 7.48 (1H, ddd, $J_{4,3}$ 8 Hz, $J_{4,5}$ 4.8 Hz, $J_{4,2}$ 0.8 Hz, 4-H), 7.71 (1H, d, $J_{5',6'}$ 5 Hz, 5'-H), 8.45 (1H, ddd, $J_{3,4}$ 8 Hz, $J_{3,2}$ 2.3 Hz, $J_{3,5}$ 1.7 Hz, 3-H), 8.72 (1H, d, $J_{6',5'}$ 5 Hz, 6'-H), 8.78 (1H, dd, $J_{5,4}$ 4.8 Hz, $J_{5,3}$ 1.7 Hz, 5-H), 9.26 (1H, dd, $J_{2,4}$ 2.3 Hz, $J_{2,3}$ 0.8 Hz, 2-H); δ_{C} (75 MHz, CDCl_3) 115.3 (d), 123.9 (d), 131.0 (s), 135.0 (d), 148.7 (d), 152.6 (d), 160.4 (d), 162.2 (s), 164.9 (s); accurate mass calculated 191.02502, found 191.02483; MS (EI) 193 (31), 192 (19), 191 (100), 190 (31), 156 (16), 129 (23), 103 (16), 76 (17), 75 (16), 51 (18), 50 (24).
- 20 Y. S. Mangutova, L. S. Mal'tseva, F. G. Kamaev, V. B. Leont'ev, S. Mukhamedkhanova, O. S. Otroshchenko and A. S. Sadykov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1973, **7**, 1510.
- 21 D. De and D. J. Krogstad, *Org. Lett.*, 2000, **2**, 879.
- 22 M. Ishikura, M. Kamada and M. Terashima, *Synthesis*, 1984, 936.
- 23 J. Sandosheim, K. Undheim and F. Rise, *Heterocycles*, 1993, **35**, 235.
- 24 Mp 31–34 °C; R_f (PE : EtOAc 2 : 1) 0.37; $\nu_{\max}/\text{cm}^{-1}$ 3060, 2966, 2936, 1610, 1570, 1514, 1432, 1247, 1181, 1028, 841, 796; δ_{H} (400 MHz, CDCl_3) 3.85 (3H, s, OCH_3), 6.99 (2H, apparent d, $J_{2,3}$ and $J_{6,5}$ 8.9 Hz, 2-H and 6-H), 7.16 (1H, dd, $J_{5',4'}$ 8.0 Hz, $J_{5',6'}$ 4.6 Hz, 5'-H), 7.72 (2H, apparent d, $J_{3,2}$ and $J_{5,6}$ 8.9 Hz, 3-H and 5-H), 7.74 (1H, dd, $J_{4',5'}$ 8.0 Hz, $J_{4',6'}$ 1.5 Hz, 4'-H), 8.56 (1H, dd, $J_{6',5'}$ 4.6 Hz, $J_{6',4'}$ 1.5 Hz, 6'-H); δ_{C} (100 MHz) 55.7 (q), 113.8 (d), 128.1 (d), 130.3 (s), 131.1 (s), 131.2 (d), 138.5 (d), 147.9 (d), 156.5 (s), 160.5 (s); accurate mass calculated 219.04509, found 219.04470; MS (EI) 221 (31), 220 (14), 219 (100), 204 (13), 184 (33), 176 (17), 141 (37), 140 (18).
- 25 Mp 96–98 °C; R_f (PE : EtOAc 2 : 1) 0.38; $\nu_{\max}/\text{cm}^{-1}$ 3007, 2925, 1610, 1516, 1255, 1022, 824, 808; δ_{H} (400 MHz, CDCl_3) 3.88 (3H, s, OCH_3), 7.04 (2H, apparent d, $J_{2,3}$ and $J_{6,5}$ 9.6 Hz, 2-H and 6-H), 7.28 (1H, d, $J_{3',2'}$ 4.4 Hz, 3'-H), 7.39 (2H, apparent d, $J_{3,2}$ and $J_{5,6}$ 9.6 Hz, 3-H and 5-H), 7.39–7.43 (1H, m, 6'-H, overlapping with anisole d at 7.39 ppm), 7.88 (1H, d, $J_{5',6'}$ 9.0 Hz, 5'-H), 8.14 (1H, d, $J_{8',6'}$ 2.1 Hz, 8'-H), 8.89 (1H, d, $J_{2',3'}$ 4.4 Hz, 2'-H); δ_{C} (100 MHz) 55.4 (q), 114.0 (d), 114.2 (d), 121.4 (d), 125.3 (s), 127.4 (d), 128.7 (s), 129.6 (s), 130.7 (d), 135.1 (s), 148.3 (s), 149.2 (s), 151.0 (d), 160.0 (s); MS (EI) 271 (27), 270 (17), 269 (100), 254 (16), 243 (10), 225 (11), 191 (38), 190 (38), 164 (12), 163 (19); CHN required C 71.25, H 4.48, N 5.19, Cl 13.13, found C 71.35, H 4.52, N 5.15, Cl 13.26.
- 26 N. Plé, A. Turck, K. Couture and G. Quéguiner, *J. Org. Chem.*, 1995, **60**, 378.
- 27 C. Gosimi, J. Y. Nedelec and J. Perichon, *Tetrahedron Lett.*, 2000, **41**, 201.