Tetrahedron 66 (2010) 2398–2403

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave-assisted synthesis of 4-amino-3,5-dihalopyridines

Mark Pichowicz [1], Simon Crumpler, Edward McDonald, Julian Blagg *

The Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Road, Belmont, Surrey SM2 5NG, UK

ARTICLE INFO

Article history:
Received 11 August 2009
Received in revised form 14 December 2009
Accepted 27 January 2010
Available online 2 February 2010

Keywords:
Amines
Coupling
Nucleophilic aromatic substitution
Pyridines
Microwave-assisted synthesis

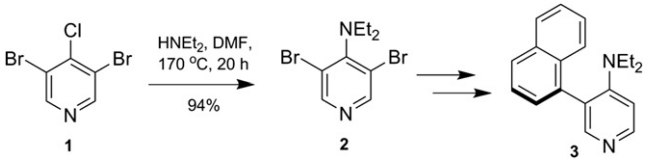
ABSTRACT

4-Amino-3,5-dihalopyridines have been efficiently prepared via microwave-assisted nucleophilic aromatic substitution of 3,4,5-trihalopyridines using 1–1.1 equiv of primary and secondary amines. The reaction is also applicable to electron rich arylamines.

1. Introduction

Recent years have seen the emergence of 4-amino-3,5-dihalopyridines as an important structural motif in medicinal chemistry; for example, as intermediates, which can be further functionalised through cross-coupling reactions[1] and as pharmaceutically active compounds across a range of disease areas.[2] Approaches to these structures often commence with 4-amino-3,5-dichloropyridine and incorporate further functionality through functionalisation of the anilino nitrogen.[3] As part of an ongoing medicinal chemistry campaign we required access to a series of 4-amino-3,5-dihalopyridines. Herein, we report a microwave-assisted coupling of 3,4,5-trihalopyridines with a range of amines, allowing rapid access to a diverse range of 4-amino-3,5-dihalopyridines.

Previously, Spivey et al. demonstrated the substitution of 3,5-dibromo-4-chloropyridine **1** with diethylamine as a key step in the preparation of chiral catalysts (Scheme 1).[4] This reaction delivered high overall yield but required heating in a sealed tube to 170 °C and a long reaction time (20 h). The resulting aminopyridine was further transformed into the atropisomeric DMAP analogue **3**. Chiral HPLC furnished enantiomerically pure (−)-**3**, which was shown to be an efficient catalyst for kinetic resolution of a series of secondary alcohols.



Scheme 1. Spivey's chiral catalyst synthesis.[4]

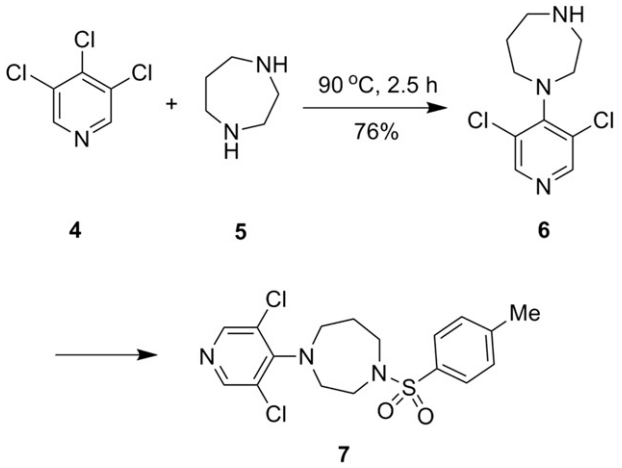
Similarly, researchers from AstraZeneca have coupled 3,4,5-trichloropyridine with 1,4-diazepane as a key step in the synthesis of 11-β-hydroxysteroid dehydrogenase inhibitors for the treatment of metabolic syndrome (Scheme 2).[5] This reaction was performed under solvent free conditions at 90 °C using 18 equiv of amine. The resultant diazepane **6** was further functionalised to deliver the sulfonamide **7**, which was shown to have an IC_{50} value of 0.91 μM versus 11-β-hydroxysteroid dehydrogenase in a competitive immunoassay.

Neither of the two approaches above was particularly suited to our needs, either requiring long reaction times and sealed tube conditions incompatible with sensitive functionality on the amine, or a large excess of the amine coupling partner, or both. Therefore we desired alternative conditions.

Metal catalysed amination of halopyridines is well precedented;[6] however, we were concerned about the regioselectivity of such an approach on our preferred substrates (**1**) and (**4**). S_NAr reactions of 2- and 4-halopyridines have been efficiently carried out under microwave conditions and we chose to follow this approach for our system. Narayan et al. used the reaction between 2-bromopyridine **8** and pyrrolidine to optimise coupling conditions. Conversion was found to be poor in water with potassium

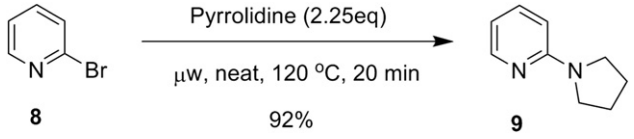
* Corresponding author. Tel.: +44 (0)20 8722 4051; fax: +44 (0)20 8722 4126.
E-mail address: julian.blagg@icr.ac.uk (J. Blagg).
[1] Present address: Departement für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012 Bern, Switzerland.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.101



Scheme 2. Synthesis of 11-β-hydroxysteroid dehydrogenase inhibitors.

carbonate as base or in toluene with triethylamine. However, the use of 2.25 equiv of pyrrolidine without added solvent led to the coupled product **9** in 92% yield (Scheme 3).[7]



Scheme 3. Microwave-assisted coupling of 2-bromopyridine **8** with amines.[7]

Similarly, 2-chloropyrimidine was coupled in good yield as was 4-chloropyridine, either as the free base or its hydrochloride salt. The reaction with piperidine was also successfully demonstrated; however, in all cases the yields were lower than with pyrrolidine. 3-Halopyridines gave very little of the desired product (<5%).[7]

When we attempted the above conditions with 4-halopyridines bearing additional halo substituents at the 3- and 5-positions as substrates, no product formation was observed. We were particularly interested in the efficient 4-substitution of 3,4,5-trihalopyridines **1** and **4** in order to maximise the opportunity for subsequent iterative diversification of the pyridine template.

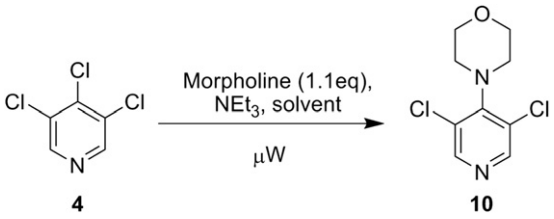
2. Results and discussion

Initially, we optimised the procedure for the S_NAr reaction of 3,4,5-trichloropyridine **4** with morpholine (1.1 equiv) using triethylamine as the base (Table 1). Reaction in ethanol at 120 °C for 30 min led to very low levels of conversion to the desired product (entry 1). Increasing the reaction temperature to 150 °C led to an approximately threefold increase in conversion (entry 2), whilst changing to the polar aprotic solvent *N*-methylpyrrolidone (NMP) led to a dramatic improvement (entry 3).[8] Further increases in the reaction temperature led to improvements in conversion (entries 4–6). Finally, heating the mixture at 220 °C for 60 min led to complete and clean conversion of the starting materials into the desired product (entry 7).

Having optimised the conditions for the reaction with morpholine (isolated yield 99%), we set about exploring the scope of the reaction. The coupling reaction proceeded smoothly with 1 equiv of other cyclic amines including pyrrolidine, piperidine and *N*-methylpiperazine to give compounds **11**, **12** and **13** in 77%, 84% and 67% yield, respectively (Table 2). Additionally, the reaction proceeded smoothly with 1.1 equiv of dimethylamine to furnish product **14** in 67% yield (Table 2).

Efficient product formation was also observed with the primary amines *n*-hexylamine and benzylamine to give compounds **15** and **17**, respectively. The introduction of bulky substituents α to the

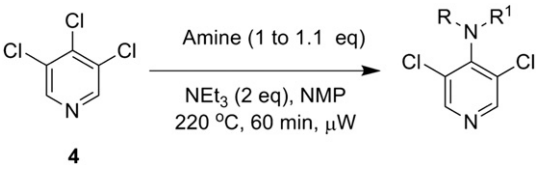
Table 1
Optimisation of conditions for the reaction between 3,4,5-trichloropyridine **4** and morpholine

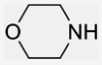
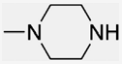
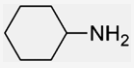
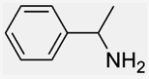
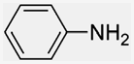


Entry	Temp (°C)	Time (min)	Solvent	Product/SM[a]
1	120	30	EtOH	1:21
2	150	30	EtOH	1:6.8
3	150	30	NMP	1.3:1
4	180	30	NMP	2.1:1
5	200	30	NMP	5.2:1
6	220	30	NMP	6.5:1
7	220	60	NMP	>99:1

[a] Determined by HPLC trace at 254 nm.

Table 2
Coupling of amines with 3,4,5-trichloropyridine **4**



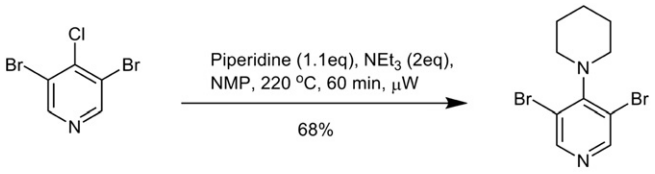
Compound/Entry	Nucleophile	Product/SM[a]	Isolated yield (%)
10		>99:1	99
11		10:1	77
12		>99:1	84
13		6:1	67
14	Me_2NH	>99:1	67
15	$CH_3(CH_2)_5NH_2$	>99:1	75
16		>99:1	92
17	$PhCH_2NH_2$	>99:1 (9.7:1)	79
18		>99:1 (102:1)	71
19		1:3 (1:9.3)	—
20	$PhCH_2OH$	1:>99	—
21	$PhCH_2SH$	1:>99	—

Values in parentheses are calculated from integration of the ^1H NMR spectra of the crude product.

[a] Determined by LCMS trace at 254 nm.

primary amine had no detrimental effect, reaction with cyclohexylamine and racemic α-methylbenzylamine both furnishing the desired products **16** and **18** in good yield. However, reaction with aniline, a poor nucleophile, led to very low levels of conversion to compound **19** (Table 2).

We attempted the reaction using benzyl alcohol and benzyl thiol (Table 2, entries 20 and 21); neither led to formation of the desired products. These results can be explained by the lower nucleophilicity of alcohols and thiols in comparison to amines.[9] 3,5-Dibromo-4-chloropyridine **1** was also coupled with piperidine (1.1 equiv) in 68% yield (Scheme 4) demonstrating that the reaction can also be performed upon this more sterically hindered system, giving rise to products, which are also versatile partners for further cross-coupling reactions.



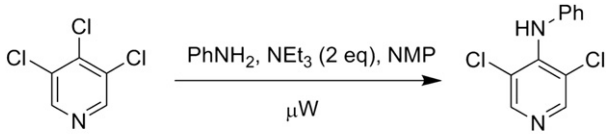
1 22

Scheme 4. Coupling of 3,5-dibromo-4-chloropyridine **1**.

In our hands a number of potentially sensitive functionalities in the amine coupling partner were tolerated, including amides, alcohols, nitriles and Cbz or acetate protected amines.[10] Amines bearing carboxylic acid or ester functionality were not tolerated due to competing self-condensation of the amine component; however, this limitation could be overcome via coupling of an appropriate nitrile followed by hydrolysis.

Following our observation that the reaction with aniline gave only a low conversion to desired product, further optimisation of the reaction conditions was performed (Table 3). Increasing the reaction temperature to 240 °C led to improved conversion (entry 2), this was further improved upon heating to 250 °C (entry 6). The use of 2 equiv of amine was also found to increase the level of conversion (entry 4), as did increasing the reaction time to 3 h (entry 7). Finally we decided upon the use of 2 equiv of aniline at 250 °C for 2 h (entry 8) as our optimal conditions.

Table 3
Optimisation of conditions for the reaction between 3,4,5-trichloropyridine **4** and aniline



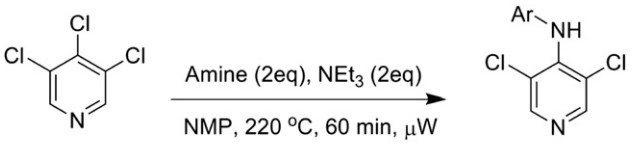
4 19

Entry	Temp (°C)	Time (min)	Aniline (equiv)	Product/SM[a]
1	220	60	1	1:2.8
2	240	60	1	1:1.6
3	240	120	1	1.5:1
4	240	60	2	1.4:1
5	250	60	1	2.3:1
6	250	120	1	3.3:1
7	250	180	1	5.5:1
8	250	120	2	6.1:1

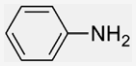
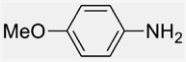
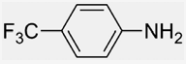
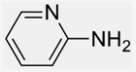
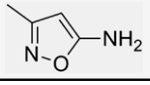
[a] Determined by HPLC trace at 254 nm.

Having optimised the conditions for the coupling with aniline to furnish the desired product in 91% yield we set about further exploring the scope of coupling with substituted anilines and heterocyclic amines (Table 4). Coupling with the electron rich 4-methoxyaniline led to excellent conversion to compound **23** as expected. However, reaction with electron deficient 4-(trifluoromethyl)aniline led to destruction of starting materials and no indication of formation of the desired product (entry 24). Similarly, attempts at coupling with the electron poor heterocyclic amines, 2-aminopyridine and 5-amino-3-methylisoxazole, led only to degradation of starting materials (entries 25 and 26).

Table 4
Coupling of anilines with 3,4,5-trichloropyridine **4**



4

Compound/Entry	Amine	Product/SM[a]	Isolated yield (%)
19		6.1:1	91
23		>99:1	66
24		1:>99	—
25		1:>99	—
26		1:>99	—

Values in parenthesis are calculated from integration of the ^{1}H NMR spectra of the crude product.
[a] Determined by LCMS trace at 254 nm.

In summary, we have developed an efficient microwave-assisted coupling reaction between 3,4,5-trihalopyridines and amines. This reaction works well for primary amines and for cyclic and acyclic secondary amines. The procedure offers the significant benefit of only requiring 1–1.1 equiv of the amine coupling partner and short reaction times. Coupling with aromatic amines is possible for electron rich systems. The products of this efficient coupling system provide versatile intermediates for subsequent iterative elaboration and these results will be published in due course.

3. General details

Microwave experiments were conducted on a Biotage Initiator Sixty™ (2.45 GHz) with automatically variable power (watt) for constant temperature control. All solvents and reagents were used as received from commercial suppliers unless otherwise stated. Compounds prepared and used subsequently without further purification were judged to be of suitable purity by NMR analysis; rt relates to the temperature range 20–25 °C. Reaction progress was monitored by thin layer chromatography (TLC) performed on polgram SIL G/UV$_{254}$ plastic backed plates or aluminium plates coated with kieselgel F$_{254}$. Visualisation was achieved by a combination of ultraviolet light (254 nm) and staining with anisaldehyde or acidic potassium permanganate. Flash chromatography was

performed using silica gel (Merck 60 (0.015–0.040 mm)), eluted with the indicated solvent.

Melting points were recorded on a Leica Galen apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum RX-I FT-IR spectrometer as dilute solutions in spectroscopic grade chloroform within a NaCl cell and are reported in cm^{-1}. Combined HPLC–MS analyses were recorded using a Waters Alliance 2795 Separations Module and Waters/Micromass LCT mass detector with electrospray ionisation (+ve or −ve ion mode as indicated). The UV detector was a Waters 2487 Dual Absorbance (254 nm).

LC–MS (6 min) analyses were performed on a Micromass LCT/Water's Alliance 2795 HPLC system with a Discovery 5 μm, C18, 50 mm×4.6 mm or 30 mm×4.6 mm i.d. column from Supelco at a temperature of 22 °C and a flow rate of 1 mL/min using a gradient elution (10:90 to 90:10 ratio) of methanol and 0.1% formic acid in water. LC–MS (3.5 min) analyses were performed on a Micromass LCT/Water's Alliance 2795 HPLC system with a Chromolith SpeedROD RP-18e 50×4.6 mm i.d. column from Merck at a temperature of 30 °C and a flow rate of 2 mL/min using a gradient elution (10:90 to 90:10 ratio) of methanol and 0.1% formic acid in water.

HPLC analyses were performed on an Agilent 1200 HPLC system with a Merck Chromolith SpeedROD RP-18e 50×4.6 mm i.d. column from Merck at a temperature of 25 °C and a flow rate of 1 mL/min using a gradient elution (0:100 to 100:0 ratio) of methanol and 0.1% formic acid in water.

NMR spectra were recorded on a Bruker AV500 machine, using $CDCl_3$ as solvent at 298 K. Chemical shifts are given in parts per million downfield from tetramethylsilane, using residual protic solvent as an internal standard. *J* values are reported in hertz and rounded to the nearest 0.5 Hz. Where required, assignments were confirmed by two-dimensional homonuclear (^1H–^1H) and heteronuclear (^1H–^{13}C) correlation spectroscopy.

3.1. General procedure A

3.1.1. Preparation of 4-(3,5-dichloropyridin-4-yl)morpholine ***10***. To a solution of 3,4,5-trichloropyridine (50 mg, 0.27 mmol) in *N*-methylpyrrolidone (NMP) (1.5 mL) were added morpholine (26 μL, 0.30 mmol) and triethylamine (76 μL, 0.54 mmol). The mixture was heated in a microwave reactor (Biotage, Initiator) at 220 °C for 60 min. After cooling to rt the mixture was poured into a saturated solution of sodium hydrogen carbonate (25 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to furnish the title compound as a white solid (63 mg, 99%), mp 55–57 °C; ν_{max} (film)/cm^{-1} 2965, 2894, 2862, 1557, 1484, 1471, 1445, 1433, 1270, 1243, 1100, 943, 588; δ_H (500 MHz, $CDCl_3$) 3.38 (4H, t, *J* 4.5, NC*H*$_2$), 3.85 (4H, t, *J* 4.5, OC*H*$_2$), 8.37 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 50.4 (CH_2), 67.4 (CH_2), 128.4 (Ar, C), 149.0 (Ar, CH), 151.0 (Ar, C); LC–MS (ESI) t_R 2.36 min, *m*/*z* 233 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_9H_{11}Cl_2N_2O$ requires 233.0243, found $[M+H]^+$ 233.0246.

3.1.2. Preparation of 3,5-dichloro-4-(pyrrolidin-1-yl)pyridine ***11***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), pyrrolidine (25 μL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 20:1) to furnish the title compound as colourless oil (46 mg, 77%); ν_{max} (film)/cm^{-1} 3287, 2959, 2929, 2869, 1561, 1472, 1451, 1402, 1088, 800; δ_H (500 MHz, $CDCl_3$) 1.97 (4H, m, NCH$_2$C*H*$_2$), 3.62 (4H, m, NC*H*$_2$), 8.27 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 25.9 (CH_2), 50.6 (CH_2), 126.7 (Ar, C), 149.1 (Ar, CH), 149.9 (Ar, C); LC–MS (ESI) t_R 2.66 min, *m*/*z* 217 (100%, M^+); *m*/*z* (ESI) $C_9H_{11}Cl_2N2$ requires 217.0295, found $[M+H]^+$ 217.0294.

3.1.3. Preparation of 3,5-dichloro-4-(piperidin-1-yl)pyridine ***12***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), piperidine (27 μL, 0.27 mmol), triethylamine (76 μL. 0.54 mmol) and NMP (1.5 mL). The crude product was purified by preparative TLC on silica gel (hexane/EtOAc, 1:1) to furnish the title compound as a colourless oil (53 mg, 84%); ν_{max} ($CHCl_3$)/cm^{-1} 2941, 2853, 1558, 1449, 1402, 1246; δ_H (500 MHz, $CDCl_3$) 1.66–1.75 (6H, m, C*H*$_2$C*H*$_2$), 3.30 (4H, t, *J* 5.5, NC*H*$_2$), 8.33 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 24.1 (CH_2), 26.5 (CH_2), 51.6 (CH_2), 128.3 (Ar, C), 149.1 (Ar, CH), 152.3 (Ar, C); LC–MS (ESI, 6 min) t_R 5.49 min, *m*/*z* 231 (100%, $[M+Na]^+$); *m*/*z* (ESI) $C_{10}H_{13}Cl_2N_2$ requires 231.0450, found $[M+H]^+$ 231.0451.

3.1.4. Preparation of 1-(3,5-dichloropyridin-4-yl)-4-methylpiperazine ***13***. General procedure A was followed using *N*-methylpiperazine (27 mg, 0.27 mmol), 3,4,5-trichloropyridine (50 mg, 0.27 mmol), triethylamine (0.76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to furnish the title compound as a colourless oil (44 mg, 65%); ν_{max} ($CHCl_3$)/cm^{-1} 2942, 2849, 2803, 1558, 1449, 1289, 1151; δ_H (500 MHz, $CDCl_3$) 2.37 (3H, d, *J* 0.5, NC*H*$_3$), 2.56 (4H, br dd, *J* 5.5, 4.0, C*H*$_2$), 3.39 (4H, br t, *J* 5.0, C*H*$_2$), 8.33 (2H, d, *J* 0.5, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 46.4 (CH_3), 50.0 (CH_2), 55.5 (CH_2), 128.4 (Ar, C), 149.2 (Ar, CH), 151.3 (Ar, C); LC–MS (ESI, 6 min) t_R 0.92 min, *m*/*z* 246 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_{10}H_{14}Cl_2N_3$ requires 246.0559, found $[M+H]^+$ 246.0560.

3.1.5. Preparation of 3,5-dichloro-N,N-dimethylpyridin-4-amine ***14***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), a 2 M solution of dimethylamine in THF (0.15 mL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to furnish the title compound as a clear colourless oil (35 mg, 67%); ν_{max} (film)/cm^{-1} 2927, 2883, 2800, 1559, 1506, 1424, 957, 810; δ_H (500 MHz, $CDCl_3$) 3.02 (6H, s, N(C*H*$_3$)$_2$), 8.30 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 42.6 (CH_3), 128.2 (Ar, C), 149.1 (Ar, CH), 152.5 (Ar, C); LC–MS (ESI, 3.5 min) t_R 2.69 min, *m*/*z* 191 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_7H_9Cl_2N_2$ requires 191.0137, found $[M+H]^+$ 191.0139.

3.1.6. Preparation of 3,5-dichloro-N-hexylpyridin-4-amine ***15***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), hexylamine (36 μL, 0.27 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to furnish the title compound as a colourless oil (51 mg, 75%); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2859, 1571, 1507, 1089; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0, C*H*$_3$), 1.30–1.62 (6H, m, C*H*$_2$), 1.62 (2H, tt, *J* 7.5, 7.0, C*H*$_2$), 3.68 (2H, dt, *J* 7.5, 6.0, C*H*$_2$), 4.73 (1H, br s, N*H*), 8.16 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 13.9 (CH_3), 22.5 (CH_2), 26.2 (CH_2), 31.0 (CH_2), 31.4 (CH_2), 45.9 (CH_2), 117.9 (Ar, C), 146.8 (Ar, C), 148.1 (Ar, CH); LC–MS (ESI, 6 min) t_R 5.24 min, *m*/*z* 247 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_{11}H_{17}Cl_2N_2$requires 247.0763, found $[M+H]^+$ 247.0762.

3.1.7. Preparation of 3,5-dichloro-N-cyclohexylpyridin-4-amine ***16***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), cyclohexylamine (35 μL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 19:1) to furnish the title compound as white solid (62 mg, 92%), mp 38–39.5 °C; ν_{max} (film)/cm^{-1} 3385, 2931, 2854, 1565, 1496, 1451, 1402, 1079; δ_H (500 MHz, $CDCl_3$) 1.26 (2H, m, C*H*H), 1.41 (2H, dddd, *J* 23.0, 11.5, 5.5, 3.5, C*H*H), 1.66 (2H, ddd, *J* 17.0, 7.5, 3.0, C*H*H),

1.78 (2H, ddd, *J* 17.0, 7.0, 4.0, C*H*H), 2.04 (2H, app dd, *J* 12.5, 3.5, C*H*H), 4.16 (1H, dddd, *J* 17.5, 10.0, 8.0, 4.0, NC*H*), 4.65 (1H, d, *J* 8.0, N*H*), 8.19 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 24.5 (CH_2), 25.5 (CH_2), 34.6 (CH_2), 53.2 (CH), 118.7 (Ar, C), 146.3 (Ar, C), 148.1 (Ar, CH); LC–MS (ESI, 3.5 min) t_R 3.03 min, *m*/*z* 245 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_{11}H_{15}Cl_2N$ requires 245.0607, found $[M+H]^+$ 245.0609.

3.1.8. Preparation of N-benzyl-3,5-dichloropyridin-4-amine ***17***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), benzylamine (33 μL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to furnish the title compound as white oily solid (55 mg, 79%); ν_{max} (film)/cm^{-1} 3394, 3278, 3030, 2925, 1568, 1496, 1453, 1403, 1083, 1062, 697; δ_H (500 MHz, $CDCl_3$) 4.89 (2H, d, *J* 6.0, CH_2Ph), 5.04 (1H, br t, *J* 6.0, N*H*), 7.33 (2H, m, Ar, C*H*), 7.36 (2H, m, Ar, C*H*), 7.39 (1H, dt, *J* 7.5, 1.5, Ar, C*H*), 8.59 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 49.9 (CH_2), 118.5 (Ar, C), 127.5 (Ar, CH), 127.9 (Ar, CH), 128.9 (Ar, CH), 138.6 (Ar, C), 146.7 (Ar, C), 148.2 (Ar, CH); LC–MS (ESI, 3.5 min) t_R 2.57 min; *m*/*z* (ESI) $C_{12}H_{11}Cl_2N_2$ requires 253.0294, found $[M+H]^+$ 253.0297.

3.1.9. Preparation of 3,5-dichloro-N-(1-phenylethyl)pyridin-4-amine ***18***. General procedure A was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), (+/−)-α-methylbenzylamine (0.39 μL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to furnish the title compound as a clear colourless oil (52 mg, 71%); ν_{max} (film)/cm^{-1} 3383, 3028, 2976, 1565, 1493, 1449, 1401, 1084, 699; δ_H (500 MHz, $CDCl_3$) 1.59 (3H, d, *J* 6.5, CH_3), 5.01 (1H, d, *J* 9.0, N*H*), 5.54 (1H, dq, *J* 9.0, 6.5, C*H*), 7.26 (1H, tt, *J* 7.0, 2.0, Ar, C*H*), 7.28 (2H, dd, *J* 7.5, 1.5, Ar, C*H*), 7.29 (2H, dd, *J* 7.5, 7.0, Ar, C*H*), 8.17 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 24.8 (CH_3), 54.4 (CH), 119.2 (Ar, C), 125.7 (Ar, CH), 127.5 (Ar, CH), 128.8 (Ar, CH), 144.0 (Ar, C), 146.3 (Ar, C), 148.1 (Ar, CH); LC–MS (ESI, 3.5 min) t_R 2.83 min; *m*/*z* (ESI) $C_{13}H_{13}Cl_2N_2$ requires 267.0451, found $[M+H]^+$ 267.0451.

3.1.10. Preparation of 3,5-dibromo-4-chloropyridine ***1***. To a solution of 4-(1*H*)-pyridone (0.95 g, 10 mmol) and potassium hydroxide (1.12 g, 20 mmol) in water (20 mL) cooled to 0 °C was added bromine (3.19 g, 20 mmmol). After stirring at this temperature for 75 min, the mixture was filtered, washed with cold water (3×50 mL) and hexane (3×20 mL) to furnish 3,5-dibromo-4-(1*H*)-pyridone as a white solid (2.09 g, 83%). This compound was used directly without further purification.

To 3,5-dibromo-4-(1*H*)-pyridone (252 mg, 1.0 mmol) was added $POCl_3$ (2 mL) and the mixture was heated at 100 °C for 2 h. The mixture was poured into ice/water (25 g) and basified by the addition of a saturated solution of sodium hydrogen carbonate. The mixture was extracted with CH_2Cl_2 (2×20 mL), the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to furnish the title compound as a white solid (275 mg, 100%), mp 101–103 °C (lit.[4] 95–96.5 °C); δ_H (500 MHz, $CDCl_3$) 8.67 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 121.9 (Ar, C), 144.2 (Ar, C), 150.8 (Ar, CH).

3.1.11. Preparation of 3,5-dibromo-4-(piperidin-1-yl)pyridine ***22***. General procedure A was followed using 3,5-dibromo-4-chloropyridine (74 mg, 0.27 mmol), piperidine (30 μL, 0.30 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 95:5) to furnish the title compound as a clear colourless oil (60 mg, 68%); ν_{max} (film)/cm^{-1} 2934, 2848, 1554, 1457, 1446, 931, 761; δ_H (500 MHz, $CDCl_3$) 1.65 (2H, dddd, *J* 9.0, 7.0, 5.5, 1.5, CH_2), 1.73 (4H, m, C*H*H), 3.26 (4H, app dd, *J* 5.5, 5.0, NC*H*H), 8.50 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 24.1 (CH_2), 26.4 (CH_2), 51.5 (CH_2), 119.7 (Ar, C), 152.2 (Ar, CH), 154.9 (Ar, C); LC–MS (ESI, 3.5 min) t_R 3.26 min, *m*/*z* 319 (100%, $[M+H]^+$); *m*/*z* (ESI) $C_{10}H_{13}Br_2ClN_2$ requires 318.9440, found $[M+H]^+$ 318.9443.

3.2. General procedure B

3.2.1. Preparation of 3,5-dichloro-N-phenylpyridin-4-amine ***19***. To a solution of 3,4,5-trichloropyridine (50 mg, 0.27 mmol) in NMP (1.5 mL) were added aniline (52 mg, 0.55 mmol) and triethylamine (76 μL, 0.54 mmol). The mixture was heated in a microwave reactor (Biotage, Initiator) at 250 °C for 60 min. After cooling to rt the mixture was poured into a saturated solution of sodium hydrogen carbonate (25 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, gradient 9:1 to 6:1) to furnish the title compound as a colourless oil (60 mg, 91%); ν_{max} (film)/cm^{-1} 3178, 3133, 3028, 2969, 1597, 1561, 1496, 1468, 1458, 1323, 1101; δ_H (500 MHz, $CDCl_3$) 6.46 (1H, s, N*H*), 6.95 (2H, dd, *J* 6.5, 0.5, Ar, C*H*), 7.14 (1H, app t, *J* 7.5, Ar, C*H*), 7.32 (2H, m, Ar, C*H*), 8.37 (2H, s, Ar, NC*H*); δ_C (125 MHz, $CDCl_3$) 121.3 (Ar, CH), 122.5 (Ar, C), 124.3 (Ar, CH), 128.9 (Ar, CH), 139.8 (Ar, C), 143.7 (Ar, C), 148.2 (Ar, CH); LC–MS (ESI) t_R 2.25 min; *m*/*z* (ESI) $C_{11}H_9Cl_2N_2$ requires 239.0143, found $[M+H]^+$ 239.0127.

3.2.2. Preparation of 3,5-dichloro-N-(4-methoxyphenyl)pyridin-4-amine ***23***. General procedure B was followed using 3,4,5-trichloropyridine (50 mg, 0.27 mmol), *p*-anisidine (75 mg, 0.55 mmol), triethylamine (76 μL, 0.54 mmol) and NMP (1.5 mL). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, gradient 9:1 to 6:1) to furnish the title compound as a colourless oil (49 mg, 66%); ν_{max} (film)/cm^{-1} 3381, 3220, 2920, 2834, 1562, 1509, 1246; δ_H (500 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.39 (1H, s, N*H*), 6.87 (2H, d, *J* 9.0, Ar, C*H*), 6.98 (2H, d, *J* 9.0, Ar, C*H*), 8.32 (2H, s, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 55.5 (CH_3), 114.1 (Ar, CH), 124.5 (Ar, CH), 132.8 (Ar, C), 144.4 (Ar, C), 148.3 (Ar, CH), 151.6 (Ar, C), 157.2 (Ar, C); LC–MS (ESI) t_R 2.33 min, *m*/*z* 269 (100%, M^+); *m*/*z* (ESI) $C_{12}H_{11}Cl_2N_2O$ requires 269.0243, found $[M+H]^+$ 269.0247.

Acknowledgements

This work was supported by Cancer Research UK grant numbers C309/A8274 and C601/A8198. We acknowledge NHS funding to the NIHR Biomedical Research Centre. We also thank Dr. Amin Mirza, Dr. Maggie Liu and Mr. Meirion Richards for their assistance with NMR and mass spectrometry.

References and notes

1. For an example see: Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513.
2. For recent examples see: (a) Geneste, H.; Oost, T.; Netz, A.; Hutchins, C. W.; Wernet, W.; Lubisch, W.; Unger, L.; Hornberger, W. PCT Int. Appl. WO 2008025735, 2008; *Chem. Abstr.* **2008**, *148*, 306179; (b) Caulkett, P. W. R.; McCoull, W.; Packer, M.; Whittamore, P. R. O. PCT Int. Appl. WO 2007122411, 2007; *Chem. Abstr.* **2007**, *147*, 46228; (c) Lewis, J. PCT Int. Appl. WO 2007115805, 2007; *Chem. Abstr.* **2007**, *147*, 502401; (d) Bissantz, C.; Grundschober, C.; Ratni, Hasane; R. -E., M.; Schnider, P. U.S. Pat. Appl. Publ. US2,007,027,163, 2007; *Chem. Abstr.* **2007**, *146*, 206339; (e) Balestra, M.; Bunting, H.; Chen, D.; Egle, I.; Forst, J.; Frey, J.; Isaac, M.; Ma, F.; Nugiel, D.; Slassi, A.; Steelman, G.; Sun, G. -R.; Sundar, B.; Ukkiramapandian, Ra.; Urbanek, R. A.; Walsh, S. PCT Int. Appl. WO2006071730 2006; *Chem. Abstr.* **2006**, *145*, 124560.
3. For an example see: Nguyen, H. V.; Motevalli, M.; Richards, C. J. *Synlett* **2007**, 725.
4. Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.
5. Caulkett, P. W. R.; McCoull, W.; Packer, M.; Whittamore, P. R. O. PCT Int. Appl. WO2007135427, 2007; *Chem. Abstr.* **2007**, *148*, 33765.
6. For leading references see: (a) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586; (b) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv.*

Synth. Catal. **2006**, *348*, 23; (c) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
7. Narayan, S.; Seelhammer, T.; Gawley, R. E. *Tetrahedron Lett.* **2004**, *45*, 757.
8. The change from protic to dipolar non-hydrogen bond donating solvents in S_NAr reactions has been demonstrated to dramatically increase the rate of reaction. For a review see: Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, NY, 2003, Chapter 5.
9. Bunnett, J. F. *Quarterly Rev. Chem. Soc.* **1958**, *12*, 1.
10. These results are part of an ongoing medicinal chemistry campaign and will be published in due course.