Tetrahedron Letters 50 (2009) 6303–6306

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Preparation of 4-heteroaryl-4-cyanopiperidines via S_NAr substitution reactions

Ronald K. Chang, Christina N. Di Marco, Daniel R. Pitts, Thomas J. Greshock *, Scott D. Kuduk

Department of Medicinal Chemistry, Merck Research Laboratories, WP 14-3, Sumneytown Pike, PO Box 4, West Point, PA 19486, USA

ARTICLE INFO

Article history:
Received 21 July 2009
Revised 27 August 2009
Accepted 28 August 2009
Available online 2 September 2009

ABSTRACT

The scope and limitations of S_NAr substitution reactions of metalated 4-cyanopiperidines with heterocyclic halides were explored. These facile reactions provide rapid access to a wide range of 4-heteroaryl-4-cyanopiperidines and have resulted in improved yields, faster reaction times, and lower temperatures than previously published synthetic methods.

The 4-arylpiperidine nucleus has proven to function as a valuable structural motif in drug discovery. These 'privileged structures' have been exploited in numerous pharmacologically relevant molecules encompassing indications such as pain (e.g., pethidine),[1,2] benign prostatic hyperplasia,[3] cancer,[4] Alzheimer's disease,[4] and anxiety (e.g., paroxetine). We recently targeted 4-heteroaryl-4-cyanopiperidines as a key functional moiety in the synthesis of bioactive molecules in the context of a neuroscience program.

Previously, 4-aryl-4-cyanopiperidines have been prepared via bis-alkylation reactions of aryl acetonitriles with N-substituted bis-(2-chloroethyl)amines (Fig. 1).[5] However, this synthetic approach proved to be inadequate for our goals as many of these reactions suffered from difficulties such as moderate to poor yields, a lack of generality, and the limited availability of substrates. Based on the known reactivity of α-lithio-cyanoenolates,[3d,6,7] we wish to report a more general and highly effective method for the preparation of 4-heteroaryl-4-cyanopiperidines via S_NAr addition of α-lithio-4-cyanopiperidine anions to recipient heteroaryl electrophiles.

Conditions to optimize the desired S_NAr reaction were explored using 2-fluoropyridine as a standard electrophile and *N*-Boc-4-cyanopiperidine. After surveying an array of bases and solvents (Table 1), it was gratifying to discover that high yields and rapid reactions were observed for most conditions examined. Both toluene and tetrahydrofuran proved to be acceptable solvents for these highly facile substitution reactions. Although an *N*-benzyl-protecting group (**1b**) on the piperidine ring (entry 2) was compatible with the reaction conditions as well, the Boc (**1a**) afforded higher yields and was suitable for a broad range of substrates (vide infra).

The scope and limitations of the S_NAr reaction were then explored in order to determine its versatility over a wide variety of substrates. Specifically, electronic and steric effects resulting from substitution about the heteroaryl electrophile were examined.

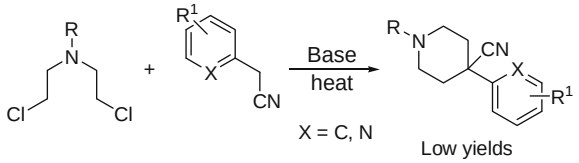
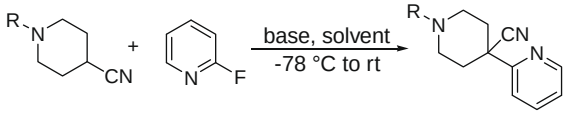


Figure 1. Bis-alkylation route to 4-heteroaryl-4-cyanopiperidines.

Table 1
S_NAr optimization



1a (R= Boc)
1b (R= Bn)

2a (R= Boc)
2b (R= Bn)

Entry[a]	Base	Solvent	Time (h)	Prod	Yield (%)
1	LiHMDS	THF	2	**2a**	89
2	LiHMDS	THF	2	**2b**	48[b]
3	LiHMDS	Toluene	2	**2a**	89
4	NaHMDS	Toluene	1	**2a**	96
5	LiHMDS	THF	0.3	**2a**	95

[a] Entries 1 and 3–5 reactant is **1a**. Entry 2 reactant is **1b**.
[b] Unoptimized yield as a small amount of unreacted 1-benzyl-piperidine-4-carbonitrile remained.

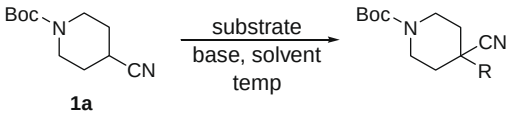
Thus, arylation of *N*-Boc-4-cyanopiperidine (**1a**) with several electronically diverse halopyridines was carried out (Table 2).[8]

Addition to electron-rich substrates such as 2-bromo-6-methoxypyridine (entry 1) and 2-chloro-4-methoxypyridine (entry 2) resulted in moderate yields when compared to more electron-deficient counterparts such as those in entries 3 and 4. Interestingly, when the anion of **1a** was subjected to 2-chloropyridine-6-carbonitrile and 2-chloropyridine-4-carbonitrile

* Corresponding author. Tel.: +1 215 652 4873; fax: +1 215 652 3971.
E-mail address: thomas_greshock@merck.com (T.J. Greshock).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.123

Table 2
Access to 4-heteroaryl-4-cyano piperidines via S_NAr chemistry



1a

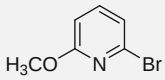
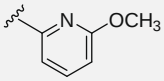
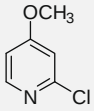
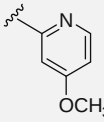
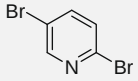
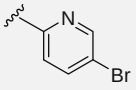
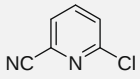
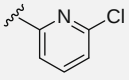
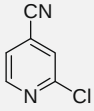
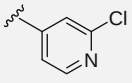
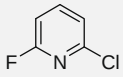
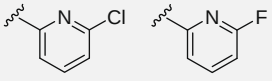
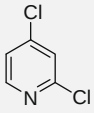
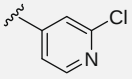
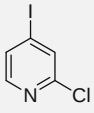
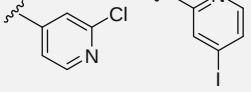
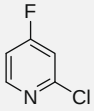
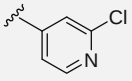
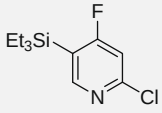
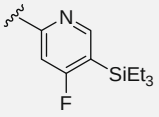
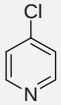
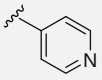
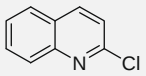
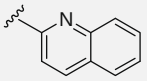
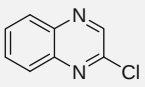
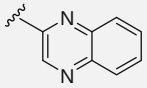
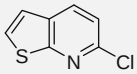
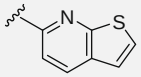
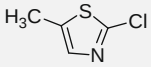
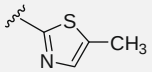
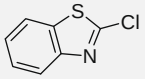
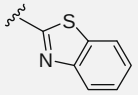
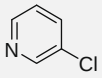
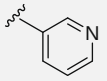
Entry	Substrate	Base	Solvent	Temp (°C)	Time (h)	R	Yield (%)
1		LiHMDS	Toluene	+23	16		66
2		LiHMDS	THF	−78 to rt	14		58
3		LiHMDS	Toluene	rt	16		100
4		LiHMDS	Toluene	−78 to rt	16		86
5		LiHMDS	THF	−76 to rt	2.5		87
6		LiHMDS	THF	−78 to rt	4		87
7		LiHMDS	THF	−76 to rt	0.5		83; trace
8		LiHMDS	THF	−78 to rt	16		81
9		LiHMDS	THF	−78 to rt	2.5		86; 2
10		LiHMDS	THF	−78 to rt	1		93
11		LiHMDS	THF	−78 to rt	36		51
12		LiHMDS	THF	−78 to rt	36		92
13		NaHMDS	THF	rt	1		60

Table 2 (*continued*)

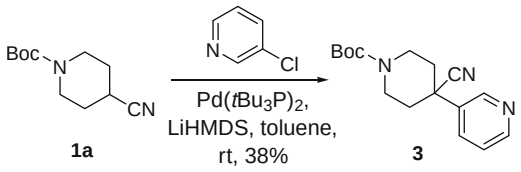
Entry	Substrate	Base	Solvent	Temp (°C)	Time (h)	R	Yield (%)
14		LiHMDS	Toluene	−78 to rt	96		75
15		NaHMDS	THF	−78 to rt	1		72
16		LiHMDS	THF	rt	1		91
17		LiHMDS	Toluene	−78 to rt	1		95
18		LiHMDS	THF	rt	48		0

(entries 5 and 6, respectively), there was no evidence of chloride displacement. Surprisingly, S_NAr occurred at the nitrile α-aromatic carbon position, resulting in the net displacement of cyanide in good yields (87%).[9] There was no evidence of products associated with nucleophilic attack on the nitrile–carbon itself.[10]

Heteroaryl electrophiles with two potentially competitive substitution sites were also examined. Not surprisingly, there was almost exclusive preference for fluoride displacement over chloride (entry 7). Interestingly, 2,4-disubstituted pyridines (entries 6, 8–10) resulted in exclusive preference for displacement at the 4-position. Even the incorporation of a more sterically encumbered and poorer leaving group at the 4-position of the pyridine, such as an iodide, only managed to afford a 2% yield of the 2-substituted pyridine product (entry 9). This inherent preference for S_NAr substitution at the 4-position of the pyridine ring can be suppressed by incorporating a sterically demanding substituent at the 5-position of the pyridine. As seen in entry 11, a triethylsilyl group[11] was used to block the 4-position, resulting in exclusive formation of the desired 2-substituted product in 51% yield. Facile desilylation can then afford the elusive 2-substituted pyridine. Direct displacement of the 4-chloropyridine (entry 12) afforded the desired material in high yield (92%).

As seen in entries 13–17, the scope of this S_NAr methodology can be expanded to a variety of hetereocycles beyond pyridines. In entries 13–15, derivatives such as quinoline, quinoxaline, and thienopyridine resulted in good yields (60–75%) of S_NAr adducts. In entries 16 and 17, S_NAr reactions with thiazole analogs afforded even higher yields.

One anticipated limitation of this methodology is its preclusion in effecting substitution reactions at the 3-position of the heteroaryl electrophile. No substitution product was observed when 3-chloropyridine was reacted with the lithium anion of *N*-Boc-4-cyanopiperidine (entry 18). To circumvent this shortcoming, transition metal-mediated cross coupling was investigated using catalytic $Pd(PtBu_3)_2$ in the reaction mixture. This strategy led to a successful palladium-catalyzed coupling of the nitrile anion with 3-chloropyridine, affording the desired pyridyl piperidine **3** in 38% unoptimized yield (Scheme 1).[12] Further work to examine the scope and potential of transition metal-catalyzed cross coupling of 4-cyanopiperidines with aryl/heteroaryl halides is underway.



Scheme 1. Bis-alkylation route to 4-heteroaryl-4-cyanopiperidines.

In summary, we have shown that the scope of S_NAr chemistry can be successfully extended to the addition of α-lithio-4-cyanopiperidines to a variety of heterocyclic electrophiles producing 4-heteroaryl-4-cyanopiperidines in moderate to quantitative yields (51–100%). In addition, unique and unexpected reactivity in S_NAr substitution reactions was observed in which a nitrile was displaced over a halide with a carbon anion. In this process, a C–C bond was broken during the S_NAr process. As far as we know, this type of selectivity for nitrile over halogen on a pyridine is unknown in the literature. This methodology has allowed facile access to 4-aryl-4-cyanopiperidines, 'priviledged structures', that have expedited our ongoing drug discovery efforts which will be communicated in a future publication.

Acknowledgments

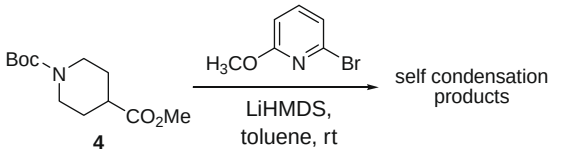
The authors would like to thank Dr. Ivory D. Hills and Mr. Robert M. DiPardo for helpful discussions.

References and notes

1. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Loti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1998**, *31*, 2235–2246.
2. (a) Carelli, V.; Cardellini, M.; Liberatore, F. *Ann. Chim.* **1959**, *49*, 709–719; (b) Buolamwini, J. K.; Knaus, E. E.. In *Drug Design and Delivery. Synthesis and Antinociceptive Activity of 4-Pyridyl and -Dihydropyridyl Analogues of Meperidine and Ketobemidone*; Harwood Academic: Great Britain, 1990; Vol. 7, pp 19–31; (c) Burkholder, T. P.; Kudlacz, E. M.; Le, T.-B.; Maynard, G. D., Substituted

Pyrrolidin-3-yl-Alkyl-Piperidines, US5824690, 20 Oct 98.; (d) Bayliss, T.; Brown, R. E.; Burkamp, F.; Jones, A. J.; Neduvelil, J. G. E-Fluoro-4-(Pyridine-2-yl)-Piperidine-1-Carboxamide Derivatives and Related Compounds Which Modulate the Function of the Vanilloid-1 Receptor (VR1) for the Treatment of Pain, WO2005/051390.

3. (a) Nagarathnam, D.; Chiu, G.; Murali Dhar, T. G.; Wong, W. C.; Marzabadi, M. R.; Cluchowski, C.; Lagu, B.; Miao, S. W. 5-(Heterocyclic Alkyl)-6-Aryl-Dihydropyrimidines, US6268369, 31 Jul 01.; (b) Patane, M. A.; DiPardo, R. M.; Newton, R. C.; Price, R. P.; Broten, T. P.; Chang, R. S. L.; Ransom, R. W.; Di Salvo, J.; Nagarathnam, D.; Forray, C.; Gluchowski, C.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2000**, 1621–1624; (c) Nantermet, P. G.; Barrow, J. C.; Selnick, H. G.; Homnick, C. F.; Freidinger, R. M.; Chang, R. S. L.; O'Malley, S. S.; Reiss, D. R.; Broten, T. P.; Ransom, R. W.; Pettibone, D. J.; Olah, T.; Forray, C. *Bioorg. Med. Chem. Lett.* **2000**, 1625–1628; (d) Blackaby, W.; Duggan, M. E.; Hallett, D.; Hartman, G. D.; Jennings, A. S.; Leister, W. H.; Lewis, R.; Lindsley, C. W.; Naylor, E.; Street, L. J.; Wang, Yi; Wisnoski, D. D.; Wolkenberg, S. E.; Zhao, Z. Heteroaryl Piperidine Glycine Transporter Inhibitors, WO2005/094514.
4. Marinier, A.; Dodier, M.; Roy, St.; Zimmermann, K.; Sang, X.; Wittman, M. D.; Landgley, D. R.; Rajamani, R. Thiazolyl Compounds Useful as Kinase Inhibitors, WO2008/124757.
5. (a) Dummel, R. J.; Wrinkle, W.; Mosher, H. S. *J. Am. Chem. Soc.* **1956**, 1936–1937; (b) Cammack, T.; Reeves, P. C. *J. Heterocycl. Chem.* **1986**, 73–75; (c) Bercz, C. V.; Ice, R. D. *J. Pharm. Sci.* **1972**, 1316–1317.
6. Klapars, A.; Waldman, J. H.; Campos, K. R.; Jensen, M. S.; McLaughlin, M.; Chung, J. Y. L.; Cvetovich, R. J.; Chen, C. *J. Org. Chem.* **2005**, *70*, 10186–10189.
7. (a) Loupy, A.; Philippon, N.; Pigeon, P.; Galons, H. *Heterocycles* **1991**, *32*, 1947–1953; (b) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712–713.
8. Typical procedure for the synthesis of 4-heteroaryl-4-cyanopiperidines: To a solution of *N*-Boc-4-cyanopiperidine (303 mg, 1.44 mmol) and 2-fluoropyridine (168 mg, 1.73 mmol) in THF (7.2 mL) at −78 °C under N_2 was added LiHMDS (2.02 mL, 2.02 mmol, 1 M in THF) dropwise. The mixture was warmed slowly to ambient temperature and stirred for 2 h. The resulting solution was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×). The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate/hexanes, 0–25%) afforded the piperidine **2a** as a white solid (373 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 4.8 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.29–7.26 (m, 1H), 4.44–4.14 (m, 2H), 3.31–3.08 (m, 2H), 2.21 (dt, J = 4.3, 13.1 Hz, 2H), 2.08–2.05 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1, 154.6, 149.9, 137.6, 123.4, 121.5, 120.8, 80.3, 45.4, 40.9, 35.1, 28.7; ES-HRMS (MNa^+) calcd for $C_{16}H_{21}N_3O_2Na$ 310.1531, found 310.1527.
9. Pratt and co-workers have observed nitrile acting as a leaving group in the 2-cyano-5-iodo-pyridine and 2-cyano-5-iodo-pyrimidine substrates: Nara, S. J.; Jha, M.; Brinkhorst, J.; Zemanek, T. J.; Pratt, D. A. *J. Org. Chem.* **2008**, *73*, 9326–9333.
10. This result was in contrast to an observation noted by Wang and co-workers who reported that the α-lithio-anion of *N*-Boc-4-methoxycarbonylpiperidine was found to condense directly with the nitrile-carbon of 2-cyano-5-bromopyridine: Wang, Y.; Nair, R. *Tetrahedron Lett.* **2007**, *48*, 1191–1193.
11. The synthesis of the 2-chloro-4-fluoro-5-(triethylsilyl)pyridine (entry 11) was prepared via the known literature method, see: Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371–1376.
12. Wang and co-workers have successfully shown the palladium-catalyzed α-arylations of *N*-Boc-4-methoxycarbonylpiperidine with various halogen-substituted pyridines (e.g., 3-chloropyridine). See Ref. 10. We have found that S_NAr reactions with *N*-Boc-4-methoxycarbonylpiperidine (**4**) led to high levels of self-condensation, which was not seen with the corresponding nitrile substrate.



Palladium-catalyzed cross coupling of ester **4** to 2-bromo-6-methoxypyridine also resulted in high amounts of self-condensation products while affording the desired product in only a 33% yield. This result was in contrast to the 94% achieved by Wang and co-workers.