Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 135–137
Tetrahedron Letters

Synthesis of *ortho*-substituted cyanopyridines through lithio intermediate trapping

Thomas Cailly, Frédéric Fabis, Stéphane Lemaître, Alexandre Bouillon and Sylvain Rault*

UPRES-EA 2126: Centre d'Etudes et de Recherche sur le Médicament de Normandie, U.F.R. des Sciences pharmaceutiques, Université de Caen Basse-Normandie, 5 rue Vaubénard 14032 Caen cedex, France

Received 11 October 2004; revised 29 October 2004; accepted 3 November 2004

Abstract—Orthолithiation of 4-cyanopyridine using 2,2,6,6-tetramethylpiperidide (LiTMP) and trapping the lithio intermediate with electrophiles represents an efficient and straightforward access to *ortho*-substituted-4-cyanopyridines. The cyano group can be used as an *ortho*-directing group and allows the preparation of 3-halogeno-4-cyanopyridines. Reactivity of 2- and 3-cyanopyridines is also investigated and seems to give similar results.

1. Introduction

The pyridine nucleus takes a wide place in natural[1] or pharmaceutical products[2] and is often used to favourably replace the benzene ring in the design of bioactive compounds. For these reasons, synthetic efforts have been made to develop methodologies towards the synthesis of functionalized pyridines. Among them, *ortho*-disubstituted pyridines represent building blocks of great importance for their use in the elaboration of fused heteroaromatic compounds.[3] Lithiation is probably one of the most powerful methods to synthesize such compounds and if metal–halogen exchange gives good results, its use is often limited by the low availability of starting materials. Ortholithiation offers an alternative to metal–halogen exchange and allows a direct and efficient access to *ortho*-disubstituted pyridines.[4] Carbon based *ortho*-directing groups such as oxazolines,[5] carboxamides[6] or lithium carboxylates[7] have been successfully used. Although the cyano group is known as an *ortho*-directing group in the lithiation of the benzene series,[8] as far we know, the ortholithiation of cyanopyridines has only been reported once on 3-cyanopyridine,[9] affording mixture of products under these conditions. Because of the potential interest of *ortho*-substituted cyanopyridines, we first experimented the lithiation and the electrophilic trapping of 4-cyanopyridines.

2. Results and discussion

In our first attempts we tried an in situ trapping method, as described by Kristensen and co-workers[10] for the benzonitrile, by adding 4-cyanopyridine in a mixture of trimethylsilyl chloride (TMSCl 2 equiv) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP 2 equiv) at −80 °C in THF. These conditions allowed us to isolate the expected monosilylated product **1a** in a 42% yield and a disilylated product **1b** in 16% yield. Increasing the reaction temperature to −40 °C and −10 °C did not permit us to improve the yield (Table 1).

Table 1. Ortholithiation and in situ trapping of 4-cyanopyridine in a one step sequence

Electrophile (2.1 equiv)	Base	Temperature (°C)	Results[a]
TMSCl	LiTMP 2 equiv	−80	**1a** (42%) **1b** (16%)
TMSCl	LiTMP 2 equiv	−40	**1a** (40%) **1b** (15%)
TMSCl	LiTMP 2 equiv	−10	**1a** (17%) **1b** (8%)
CBr_4	LiTMP 2 equiv	−80	Starting material
I_2	LiTMP 2 equiv	−80	Starting material

[a] Isolated yields.

Keywords: Cyanopyridine; Ortholithiation; Electrophile; *ortho*-Substituted pyridine.
* Corresponding author. Tel.: +33 2 31 93 41 59; fax: +33 2 31 93 11 59; e-mail: rault@pharmacie.unicaen.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.021

Unfortunately, switching the electrophile TMSCl for CBr_4 (2.1 equiv) and I_2 (2.1 equiv), only starting materials were recovered, probably due to the reaction of LiTMP with CBr_4 and I_2. In order to avoid this problem we came back to a classical lithiation method. LiTMP (1 equiv) and 4-cyanopyridine were reacted before addition of TMSCl (2.1 equiv) at −80 °C in THF. Under these conditions we only recovered the unchanged starting materials. By using 2 equiv of LiTMP, we were able to isolate two products: a monosilylated one **1a** in 66% yield and a disilylated **1b** one in 17% yield. These results showed that the first equivalent of LiTMP does not react as a base despite its hindering but by addition to the nitrile group. This intermediate was then ortholithiated with the second equivalent of LiTMP as described by Krizan and Martin with the isopthalonitrile.[8]

The same conditions were used with the cheaper lithium diisopropylamide (LDA), that is also a weaker and a less hindered base, but the reaction gave us a complex mixture of starting materials, monosilylated and disilylated products in trace amounts and other unidentified aromatic compounds (Table 2).

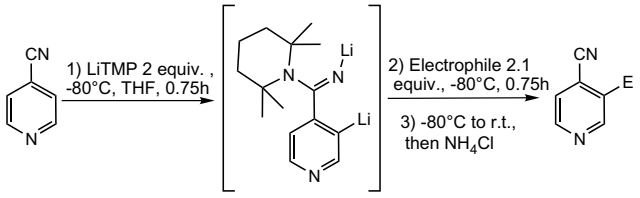
We then extended the reaction to other electrophiles with our best conditions: ortholithiation of 4-cyanopyridine with 2 equiv of LiTMP and then trapping with different electrophiles (Scheme 1, Table 3).[11]

Halogenation of 4-cyanopyridine was realized with I_2, CBr_4 and C_2Cl_6. Iodine gave us two products, 3-iodoisonicotinonitrile **2a** and 3,5-diiodoisonicotinonitrile **2b** in, respectively, 54% and 14% yield, while carbon tetrabromide and hexachloroethane gave only monohalogenation products, 3-bromoisonicotinonitrile **3** in 69% yield and 3-chloroisonicotinonitrile **4** in 75% yield, respectively. The presence of a second lithiation, while using TMSCl and I_2 could be explained by an homotransmetalation type mechanism.[12]

Table 2. Ortholithiation and trapping of 4-cyanopyridine in a two steps sequence

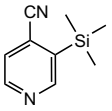
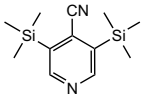
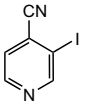
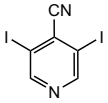
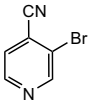
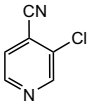
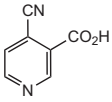
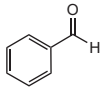
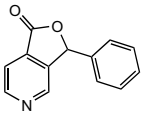
Electrophile (2.1 equiv)	Base	Temperature (°C)	Results[a]
TMSCl	LiTMP 1 equiv	−80	Starting material
TMSCl	LiTMP 2 equiv	−80	**1a** (66%) **1b** (17%)
TMSCl	LDA 2 equiv	−80	**1a**, **1b** Traces

[a] Isolated yields.



Scheme 1. Ortholithiation and trapping of 4-cyanopyridine in a two steps sequence.

Table 3. Ortholithiation and trapping of 4-cyanopyridine in a two step sequence at −80 °C, using 2 equiv of LiTMP and various electrophiles[a]

Electrophiles	Products	Yields (%)	Product number
Me_3SiCl		66	**1a**
		17	**1b**
I_2		54	**2a**
		14	**2b**
CBr_4		69	**3**
C_2Cl_6		75	**4**
CO_2		41	**5**
		70	**6**

[a] Isolated yields.

Carboxylation with dry ice permitted us to isolate 4-cyanoisonicotinic acid **5** in 41% yield. This moderate yield was certainly due to the zwitterionic form of this compound which made it partly hydrosoluble and difficult to isolate from the aqueous phase. Benzaldehyde did not give the expected alcohol but the lactone **6** in a 70% yield.

We then extended the method with 2- or 3-cyanopyridine. Trapping the lithio intermediate with iodine gave as for 4-cyanopyridine a mixture of mono and diiodo compounds in similar yields. With hexachloroethane, 2-cyanopyridine gave the expected 2-chloro-3-cyanopyridine **9** in a 75% yield, whereas 3-cyanopyridine gave a hard to separate mixture of 4-chloro-3-cyanopyridine **10a** and 2-chloro-3-cyanopyridine **10b** in a 4:1 ratio as determined by ^1H NMR (see Table 4).

3. Conclusion

In conclusion, we have described an efficient method for the one step synthesis of *ortho*-substituted cyanopyridines with moderate to good yields. The cyano group

Table 4. Ortholithiation and trapping of 2- or 3-cyanopyridine in a two step sequence at −80 °C, using 2 equiv of LiTMP and I_2 or C_2Cl_6 as electrophiles

Cyano group position	Electrophiles	Products	Yields[a] (%)	Product number
2	I_2		52	**7a**
			19	**7b**
3	I_2		56	**8a**
			17	**8b**
2	C_2Cl_6		75	**9**
3	C_2Cl_6		37	**10a**
			7	**10b**

[a] Isolated yields.

was used as an *ortho*-directing group for the lithiation in the pyridine series and allowed a facile access to new or difficult to synthesize pyridine compounds.

Acknowledgements

We thank Servier laboratories, the 'Conseil Régional de Basse-Normandie' for financial support and Mr. Yves Dat for mass spectroscopy.

References and notes

1. (a) Volk, C. A.; Köck, M. *Org. Lett.* **2003**, *5*, 3567–3569; (b) Núñez, M. J.; Guadaño, A.; Jiménez, I. A.; Ravelo, A. G.; González-Coloma, A.; Bazzochi, I. L. *J. Nat. Prod.* **2004**, *67*, 14–18; (c) Jayasuriya, H.; Herath, K. B.; Ondeyka, J. G.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Springer, M. S.; Siciliano, S.; Malkowitz, L.; Sanchez, M.; Guan, Z.; Tiwari, S.; Stevenson, D. W.; Borris, R. P.; Singh, S. *J. Nat. Prod.* **2004**, *67*, 1036–1038; (d) Bouillon, A.; Voisin, A. S.; Robic, A.; Lancelot, J. C.; Collot, V.; Rault, S. *J. Org. Chem.* **2003**, *68*, 10178–10180; (e) Guillier, F.; Nivoliers, F.; Bourguignon, J.; Dupas, G.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1992**, *33*, 7355–7356.
2. (a) Chen, C.; Wilcoxen, K. M.; Huang, C. Q.; Xie, Y. F.; McCarthy, J. R.; Webb, T. R.; Zhu, Y. F.; Saunders, J.; Liu, X. J.; Chen, T. K.; Bozigian, H.; Grigoriadis, D. E. *J. Med. Chem.* **2004**, *47*, 4787–4798; (b) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645–4648.
3. (a) Watanabe, M.; Shinoda, E.; Shimizu, Y.; Furukawa, S. *Tetrahedron* **1987**, *43*, 5281–5286; (b) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292–296; (c) Ferraris, D.; Ko, Y. S.; Pahutski, T.; Ficco, R. P.; Serdyiuk, L.; Alemu, C.; Bradford, C.; Chiou, T.; Hoover, R.; Huang, S.; Lautar, S.; Liang, S.; Lin, Q.; Lu, M. X. C.; Mooney, M.; Morgan, L.; Qian, Y.; Tran, S.; Williams, L. R.; Wu, Q. Y.; Zhang, J.; Zou, Y.; Kalish, V. *J. Med. Chem.* **2003**, *46*, 3138–3151.
4. Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
5. Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633–2637.
6. (a) Epsztajn, J.; Zbnigniew, B.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739–4742; (b) Epsztajn, J.; Bienik, A.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735–4738; (c) Epsztajn, J.; Brzezinski, J. Z.; Jozwiak, A. *J. Chem. Res. (s)* **1986**, 18–19; (d) Epsztajn, J.; Bienik, A.; Plokta, M. W. *J. Chem. Res. (s)* **1986**, 20–21.
7. (a) Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 5483–5486; (b) Lazaar, J.; Rebstock, A. S.; Mongin, F.; Godard, A.; Trécourt, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 6723–6728.
8. (a) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681–2682; (b) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157.
9. Petnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276–9287.
10. Kristensen, J.; Lysén, M.; Vedso, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435–1437.
11. Typical procedure: To a stirred solution under N_2 of 2,2,6,6-tetramethylpiperidine (20.2 mmol, 3.4 mL) in THF (40 mL) was added at −30 °C 2.5 M *n*-butyllithium (19.2 mmol, 7.7 mL). The solution was allowed to reach 0 °C, kept under stirring during 15 min and cooled to −80 °C. 4-Cyanopyridine (9.6 mmol, 1 g) in THF (20 mL) was slowly added to the mixture over 15 min. After 30 min of stirring at −80 °C, a solution of hexachloroethane (20.2 mmol, 4.78 g) in THF (10 mL) was slowly added over 15 min and the resulting mixture stirred for 30 min. The solution was then allowed to warm slowly to room temperature. The mixture was quenched with 40 mL of a saturated NH_4Cl solution. The solution was extracted with EtOAc (3 × 100 mL), the combined organic layers were washed with brine (2 × 100 mL), dried with $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified by silica gel chromatography using EtOAc/cyclohexane (1:4) as eluent to afford 3-chloroisonicotinonitrile **4** (0.99 g, Yield: 75%) as pale orange needles. 3-Chloroisonicotinonitrile **4**: ^1H NMR (400 MHz, $CDCl_3$) 7.56 (d, $^3J = 4.8$ Hz, 1H), 8.68 (d, $^3J = 4.8$ Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 113.7, 120.9, 126.3, 133.1, 148.1, 150.4; IR (KBr) 3016, 2953, 2475, 2238 (CN), 1573, 1471, 1401, 1384, 1280, 1162, 1036, 840, 795, 708, 576 cm^{-1}; mp 80 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22; found C, 52.39; H, 2.37; N, 20.32.
12. Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *16*, 3433–3440.