COMMUNICATION

# Synthesis of 2-heteroaryl-3-hydroxypyridines by ring expansion reactions of 2-acylfurans with ammonia

**Richard W. J. Chubb,[a] Martin R. Bryce *[a] and Brian Tarbit [b]**

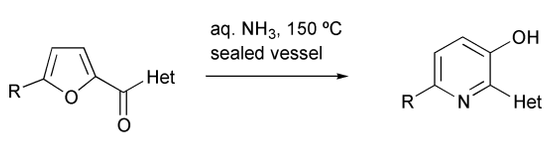
[a] *Department of Chemistry, University of Durham, Durham, UK DH1 3LE. E-mail: m.r.bryce@durham.ac.uk*
[b] *Seal Sands Chemicals Ltd., Seal Sands Road, Seal Sands, Middlesbrough, UK TS2 1UB*

***Received (in Cambridge, UK) 14th June 2001, Accepted 9th July 2001***
***First published as an Advance Article on the web 19th July 2001***

**A straightforward and versatile synthesis of 2-heteroaryl-3-hydroxypyridine derivatives is described by the one-step reaction of 2-acylfurans with ammonia at 150 °C.**

Heteroaryl-substituted pyridine derivatives, including bipyridyls, are a very important family of compounds in diverse areas of chemistry such as metal-coordination complexes,[1] supramolecular assemblies,[2] pharmaceutical agents,[3] natural products[4] and molecular electronic device materials.[5] The vast majority of syntheses of heteroaryl- (or aryl-) substituted pyridines involve metal-catalysed cross-coupling reactions of the Stille or Suzuki type.[6] A few non-coupling procedures have been developed, but they are generally applicable only to a limited range of ring systems and substituents. Examples are: (i) cyclisation of a substituent which is attached to the pyridine ring (*e.g.* thioamide → thiazole);[1a] (ii) reaction of a lithioheterocycle with a pyridinium cation;[7] (iii) oxidation of a 2-heteroaryl-5-(phenylseleno)-3,4,5,6-tetrahydropyridine derivative.[8]

In the context of non-coupling routes to biaryls we were attracted to the work of Leditschke who reported in 1952 that 2-benzoylfuran (**1**, Het = Ph; R = H) reacted with ammonia to give 2-phenyl-3-hydroxypyridine. The proposed mechanism involves initial attack of ammonia at C-5 of the furan, leading to a ring opening–ring closure sequence, and the furan oxygen becomes the hydroxy group in the product.[9] Gruber extended this route to substituted phenyl substituents.[10] However, this reaction is essentially unexplored as a route to bi(heteroaryl) systems, although it has been established that the reaction will proceed with Het = dibenzofuran[11] and 2- and 4-pyridyl substituents.[12] We now report that this methodology is considerably more versatile than has been realised hitherto, and it provides a general route to a range of 2-heteroaryl-3-hydroxypyridine derivatives **2a**–**l** (Scheme 1 and Table 1).




**1** **2**

**Scheme 1**

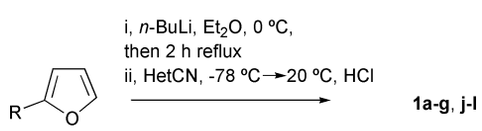
The precursor acylfuran derivatives **1a**–**l** were readily obtained as shown in Schemes 2–4. Lithiation of furan or 2-methylfuran **3**, followed by reaction with the appropriate cyano-substituted heterocycle, afforded compounds **1a**–**g**,**j**–**l** in 42–76% yields (Scheme 2). Compound **1h** was obtained (30% yield) by selective lithiation of 2,5-dibromopyridine **4** at C-5[13] and reaction with 2-cyanofuran (Scheme 3) and compound **1i** was prepared (42% yield) by the literature route from di-2-furylmethanol **5** (Scheme 4).[14]

Reaction of **1a**–**l** with aqueous ammonia at 150 °C in a sealed tube afforded products **2a**–**l** in the yields shown after purification in Table 1. Although these yields are only low or moderate, the reaction has many attractive and viable features from a synthetic viewpoint: (i) the starting furan derivatives **1a**–**l** are readily accessible from commercial reagents; (ii) it is usually straightforward to obtain analytically pure products **2** by a single recrystallisation of the crude product mixture (see Experimental below); (iii) the reaction proceeds with both electron-deficient (*e.g.* pyridyl, quinolyl, pyrazinyl) and electron-rich (*e.g.* furyl, indolyl) Het substituents; (iv) the products **2** carry a 3-hydroxy substituent which would not be tolerated by

**Table 1** Compounds **2a**–**l** obtained by the route shown in Scheme 1

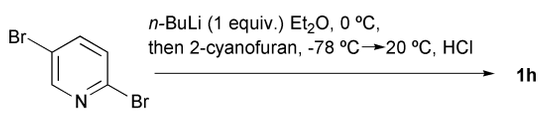
| | Het | R | Yield (%)[a] | Mp/°C |
|---|---|---|---|---|
| **a** | 2-Pyridyl | H | 18 | 30–32 |
| **b** | 2-Pyridyl | Me | 25 | 60–62 |
| **c** | 3-Pyridyl | H | 37 | 171–173 |
| **d** | 3-Pyridyl | Me | 27 | 195–196 |
| **e** | 4-Pyridyl | H | 35 | 234–236 |
| **f** | 4-Pyridyl | Me | 31 | 257–260 |
| **g** | 2-Me-5-pyridyl | H | 15 (27)[b] | 181–183 |
| **h** | 2-Br-5-pyridyl | H | 26 | 167–169 |
| **i** | 2-Furyl | H | 17 | 210–212 |
| **j** | 3-Quinolyl | H | 26 | 181–184 |
| **k** | 5-Indolyl | H | 12 | 141–143 |
| **l** | Pyrazin-2-yl | H | 20 | 87–89 |

[a] Yields refer to analytically pure product fully characterised by spectroscopic data after recrystallisation or column chromatography. [b] Yield obtained from reaction at 110 °C for 12 h.



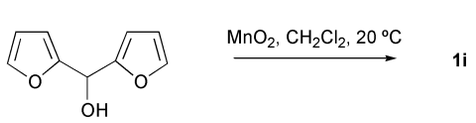

**3** R = H or Me

**Scheme 2**




**4**

**Scheme 3**




**5**

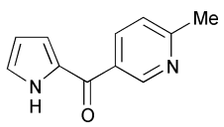
**Scheme 4**

DOI: 10.1039/b105228b


**This journal is © The Royal Society of Chemistry 2001**

standard metal-catalysed cross-coupling routes, or other non-coupling routes without use of a protecting group.

We have found that the most widely applicable reaction conditions are 150 °C for 5 h. Although the yield of the pyridine products **2** can be raised by using a lower reaction temperature, this benefit is offset by the formation of more by-products which complicated the work-up procedure. For example, a detailed study of the conditions for **1g** established that reaction at 110 °C for 12 h gave **2g** in 27% yield along with the pyrrolyl pyridyl ketone derivative **6** (16% yield) which were separated chromatographically.




**6**

It is also significant that the presence of the 5-methyl substituent R in **1b**, **d** and **f** does not hinder the ring-expansion reaction. This augers well for the use of more highly functionalised furans as precursors to new 3-hydroxypyridine derivatives[15] with otherwise inaccessible substitution patterns.

## Experimental

A mixture of compound **1** (2.5 mmol) and aqueous ammonia solution (0.880, 2 $cm^3$) was heated in a sealed thick-walled glass Carius tube at 150 °C for 5 h. The tube was cooled, water and methanol were added and the crude product mixture was evaporated *in vacuo* to yield a brown gum. Trituration with acetone or ether gave a brown solid which was recrystallised to afford product **2**, or chromatographed on an alumina column with ethyl acetate as eluent. Spectroscopic and analytical data are entirely consistent with their structures.

## Acknowledgements

We thank Seal Sands Chemicals Ltd. for funding this work.

## References

1 (*a*) C. R. Rice, S. Wörl, J. C. Jeffrey, R. L. Paul and M. D. Ward, *J. Chem. Soc., Dalton Trans.*, 2001, 550; (*b*) S. S. Zhu, R. P. Kingsborough and T. M. Swager, *J. Mater. Chem.*, 1999, **9**, 2117; (*c*) P. Pickup, *J. Mater. Chem.*, 1999, **9**, 1641.
2 A. Ranganathan, V. R. Pedireddi, S. Chatterjee and C. N. R. Rao, *J. Mater. Chem.*, 1999, **9**, 2407.
3 (*a*) W. J. Thompson, J. H. Jones, P. A. Lyle and E. J. Thies, *J. Org. Chem.*, 1988, **53**, 2052; (*b*) M. Ishikura, M. Kamada and M. Terashima, *Synthesis*, 1984, 936.
4 M. Tiecco, M. Tingoli, L. Testaferri, D. Chainelli and E. Wenkert, *Tetrahedron*, 1986, **42**, 1475.
5 (*a*) U. Mitschke and P. Bäuerle, *J. Mater. Chem.*, 2000, **10**, 1471; (*b*) C. Wang, C.-Y. Jung, Y. Hua, C. Pearson, M. R. Bryce, M. C. Petty, A. S. Batsanov, A. E. Goeta and J. A. K. Howard, *Chem. Mater.*, 2001, **13**, 1167.
6 (*a*) Review: S. P. Stanforth, *Tetrahedron*, 1997, **54**, 263; (*b*) N. Zhang, L. Thomas and B. Wu, *J. Org. Chem.*, 2001, **66**, 1500; (*c*) M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet and M. Santelli, *Chem. Commun.*, 2001, 325; (*d*) J. J. Li and W. S. Yue, *Tetrahedron Lett.*, 1999, **40**, 4507.
7 M.-J. Shiao, L.-H. Shih, W.-L. Chia and T.-Y. Chan, *Heterocycles*, 1991, **32**, 2111.
8 M. Tingoli, M. Tiecco, L. Testaferri, R. Andrenacci and R. Balducci, *J. Org. Chem.*, 1993, **58**, 6097.
9 H. Leditschke, *Chem. Ber.*, 1952, **85**, 202.
10 (*a*) W. Gruber, *Chem. Ber.*, 1955, **88**, 178; (*b*) W. Gruber, *Chem. Ber.*, 1955, **88**, 185.
11 H. Leditschke, *Chem. Ber.*, 1953, **86**, 612.
12 C. A. Lipinski, J. L. LaMattina and P. J. Oates, *J. Med. Chem.*, 1986, **29**, 2154.
13 C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.
14 N. A. Bugamin, Y. V. Gulevich and I. P. Beletskaya, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Trans.)*, 1984, **33**, 2600.
15 3-Hydroxypyridine derivatives have many important pharmacological properties: *e.g.* (*a*) nikkomyzin Z (antifungal): A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, H. Gurzik and A. K. Ganguly, *Tetrahedron Lett.*, 1993, **34**, 3267; (*b*) cicletanine (antihypertensive): L. Kalinowski, I. T. Dobrucki and T. Malinski, *J. Cardiovasc. Pharmacol.*, 2001, **37**, 713; (*c*) pantoprazole (antiulcer): H. Terauchi, A. Tanitame, K. Tada, K. Nakamura, Y. Seto and Y. Nishikawa, *J. Med. Chem.*, 1997, **40**, 313.