ORGANIC LETTERS

2005
Vol. 7, No. 25
5661−5664

Tandem Directed Lithiations of *N*-Boc-1,2-dihydropyridines toward Highly Functionalized 2,3-Dihydro-4-pyridones

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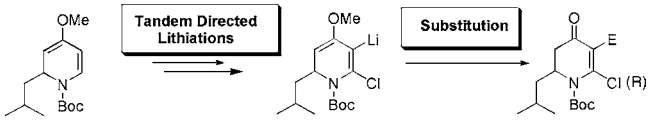
Received September 23, 2005

ABSTRACT



Sequential tandem directed lithiations of an *N*-Boc-4-methoxy-1,2-dihydropyridine have been achieved, leading to C-5,C-6 disubstituted dihydropyridones on acidic workup. The chlorine atom of the dihydropyridone products can in turn be substituted giving rise to diverse substituents at C-6.

Nitrogen-containing heterocycles are profoundly represented among natural products and pharmaceutically relevant small molecules.[1] Methods aimed at achieving such compounds with strict control of regio- and stereochemistry continue to stand as a prominent objective in synthetic organic chemistry. In this vane, the 2,3-dihydro-4-pyridone **1** has been revealed as an important synthetic building block in the synthesis of several classes of azaheterocycles (Figure 1).[2]

These dihydropyridones have proficiently served as precursors to piperidine, perhydroquinoline, quinolizidine, and indolizidine skeletons.[2,3] Moreover, the value of these compounds is significantly enhanced by the facility to construct them enantiomerically pure (**1b**) invoking methods emanating from our laboratories and others.[4] As part of our ongoing efforts to illustrate the versatility of dihydropyri-

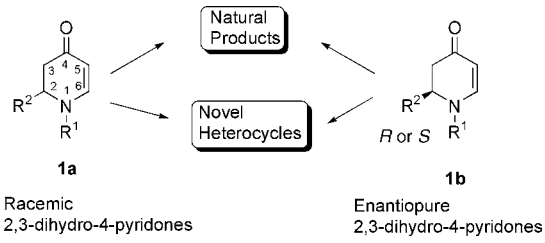


Figure 1. Synthetic utility of dihydropyridones **1**.

(1) (a) Cordell, G. A. *The Alkaloids*: *Chemistry and Biology*; Elsevier Science: San Diego, CA, 2003; Vol. 60. (b) Hesse, M. *Alkaloids*: *Nature's Curse or Blessing*?; Wiley-VCH: Weinheim, Germany, 2003. (c) Southon, I. W.; Buckingham, J. *Dictionary of Alkaloids*; Chapman & Hall: London, UK, 1989.

(2) (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press Inc.: Greenwich, CT, 1996; Vol. 2, p 251. (b) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; McKillop, A., Ed.; Pergamon Press: Oxford, England, 1996; Vol. 5, p 37. (c) Comins, D. L. *J. Heterocycl. Chem.*, **1999**, *36*, 1491. (d) Joseph, S. P.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870.

(3) For recent examples and leading references, see: (a) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863. (b) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219. (c) Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A. *J. Org. Chem.* **2005**, *70*, 5221.

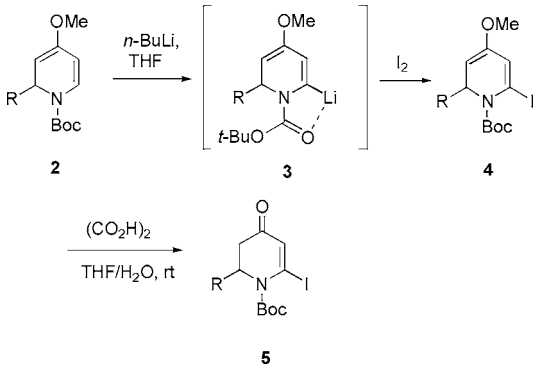
(4) Through chiral 1-acylpyridinium salts, see: (a) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1994**, *35*, 7343. (d) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651. (e) Ege, M.; Wanner, K. T. *Org. Lett.* **2004**, *6*, 3553 and references therein. (f) For examples of asymmetric hetero Diels−Alder reactions, see: (g) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (h) Waldmann, H. *Synthesis* **1994**, 535.

10.1021/ol052313a CCC: $30.25
Published on Web 11/08/2005

dones toward the generation of more elaborate natural and biologically active substances, we desired a means for a facile entry into more highly substituted derivatives. To address this goal, we describe herein the preparation of 5,6-disubstituted 2,3-dihydro-4-pyridones emanating from a sequence of tandem directed lithiations of *N*-Boc-1,2-dihydropyridines.

The directed ortho metalation (DoM) reaction is an effective platform for functionalization of aromatic compounds with controlled regiochemical outcomes.[5] Utilized to a lesser extent is the related DoM of nonaromatic substrates. One example of such is the α-lithiation of *N*-Boc-1,4-dihydropyridines that was first reported by us.[6] This methodology provides an expedient and controlled access to substituted 1,4-dihydropyridines and pyridines. These seminal studies led to application of the lithiation methodology to the related *N*-Boc-4-methoxy-1,2-dihydropyridines, which are effectively converted to 2,3-dihydro-4-pyridones on acidic workup.[7] In this case, treatment of the *N*-Boc-1,2-dihydropyridine **2** with *n*-BuLi generates the C-6 lithiated intermediate **3** (Scheme 1). Quenching of this anion with I_2,

Scheme 1

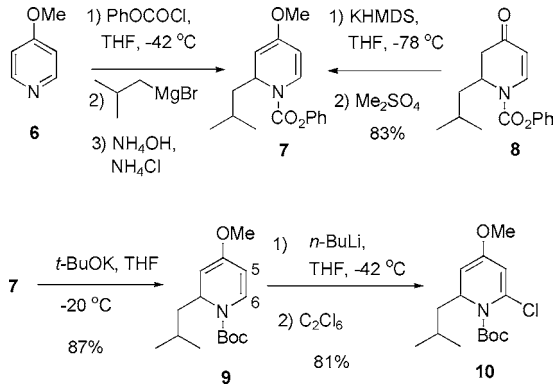


followed by mild acidic hydrolysis of the enol ether, gives the 6-iodo-2,3-dihydro-4-pyridone **5**.

These 6-iodo derivatives were found by us to be effective coupling partners in Sonogashira reactions.[8] We sought to build upon these methodologies to gain a facile entry into more elaborately functionalized dihydropyridones. We surmised that if a suitable directing group was affixed at the C-6 position of the dihydropyridine by the previous protocol, a second lithiation event at C-5 might then be feasible by addition of another equivalent of an alkyllithium base. Although the C-5 position of a 1,2-dihydropyridine is electron rich, potentially abrogating deprotonation there, it was rationalized that the directing pressure of two adjacent groups would render this lithiation possible. On the basis of its well-documented aptitude for such reactivity in aromatic systems,[5b] a chlorine atom was elected as a suitable candidate at the C-6 position to appropriately confer this directing ability.

To test this tandem lithiation hypothesis, dihydropyridine **7** was prepared through formation of an *N*-acylpyridinium salt with 4-methoxypyridine and phenyl chloroformate followed by treatment with isobutylmagnesium bromide (Scheme 2). A carbamate exchange to the more hindered *N*-Boc

Scheme 2



derivative was effected with *t*-BuOK in THF to furnish dihydropyridine **9**.[8,9] This expedient route to **7** belies direct administration to our preparation of enatiomerically pure dihydropyridones.[4] Utilization of this asymmetric technology necessarily proceeds through the dihydropyridone first to allow facile removal of the chiral auxiliary. We therefore optimized conditions to obtain **7** via O-methylation of the dihydropyridone itself. After some effort, it was discovered that treatment with dimethyl sulfate following enolization of dihydropyridone **8** with KHMDS at −78 °C in THF rendered dihydropyridine **7** in good yield. This reaction can suitably be used to generate enantiomerically pure 4-methoxy-1,2-dihydropyridines from nonracemic dihydropyridones **1b**. The C-6 directed lithiation and chlorination sequence was executed by treatment of **9** with *n*-BuLi followed by hexachloroethane to afford the 6-chlorodihydropyridine **10** in 81% yield (Scheme 2). This transformation was particularly valuable given that other chlorinating agents examined in this reaction (*N*-chlorosuccinimide, trifluoromethylsulfonyl chloride) rendered extensive decomposition. Accordingly, through this directed lithiation, we were able to install the directing group of choice and pave the way for a potential second reaction of this type at C-5.

Efforts were now directed at the C-5 metalation and functionalization of **10**. Deprotonation of the chlorodihydropyridine was first probed by a deuterium quenching experiment (Scheme 3). In the initial attempt, dihydropyridine **10** was treated with *n*-BuLi at −78 °C, quenched with deuterium oxide, and then warmed to ambient temperature. Gratifyingly, a mild hydrolysis of the reaction mixture with

(5) Directed ortho metalation: (a) Gwensh, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Sniekus, V. *Chem. Rev.* **1990**, *90*, 879.

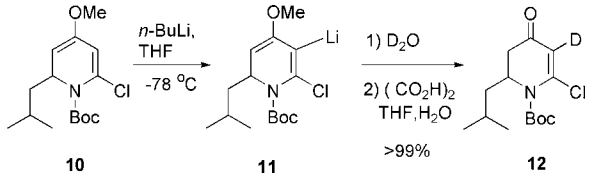
(6) (a) Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807. (b) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437.

(7) (a) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053. (b) For a related metalation, see: Comins, D. L.; Weglarz, M. A.; O'Connor, S. *Tetrahedron Lett.* **1988**, *29*, 1751.

(8) Comins, D. L.; Williams, A. L. *Org. Lett.* **2001**, *3*, 3217.

(9) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.

Scheme 3

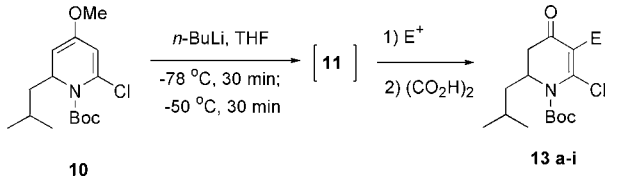


aqueous oxalic acid resulted in isolation of **12** as the only product. The complete incorporation of deuterium into C-5 indicated that the DoM was complete and highly regioselective.

Regarding the mechanism of this transformation, we conjecture that a kinetic and synergistic directing influence of *both* the C-4 methoxy and C-6 chloro groups in **10** attribute to the selective lithiation at C-5. It cannot be ruled out, however, that deprotonation initially occurs elsewhere and then equilibrates to C-5 owing to the thermodynamic charge stabilizing effect of situating the anion between two positively polarized carbon atoms.[10] This reaction, to the best of our knowledge, constitutes the first demonstration of a C-5 directed metalation on dihydropyridine substrates.

Encouraged by these preliminary results, we moved to apply this methodology toward the installation of a range of functional groups at C-5 (Table 1).

Table 1. Preparation of Dihydropyridones **13** from Dihydropyridine **10**



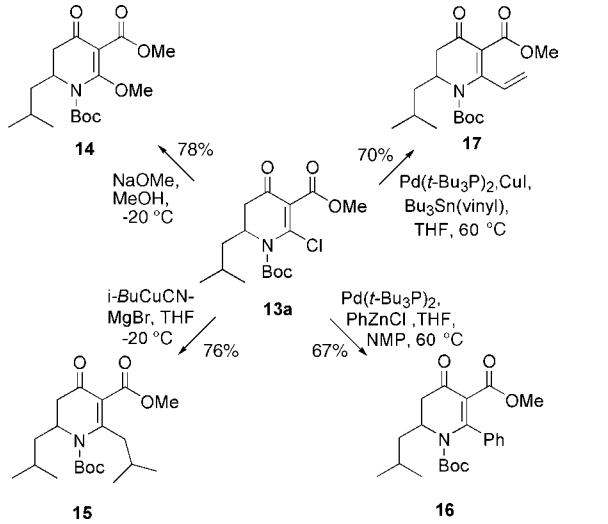
entry[a]	electrophile (E+)	product, E	yield[b] (%)
1	$ClCO_2Me$ (4.0 equiv)	**13a**, CO_2CH_3	77
2	MeSSMe (1.5 equiv)	**13b**, SMe	87
3	PhSeSePh (1.5 equiv)	**13c**, SePh	62
4	I_2 (1.5 equiv)	**13d**, I	91
5	C_2Cl_6 (1.5 equiv)	**13e**, Cl	88
6	PhCHO (1.5 equiv)	**13f**, CH(OH)Ph	67[c]
7	DMF (1.5 equiv)	**13g**, CHO	43
8	Ac_2O (1.5 equiv)	**13h**, $COCH_3$	71
9	CH_3CH_2I (5.0 equiv)	**13i**, CH_2CH_3	56

[a] The reactions were generally performed on a 1−3.0 mmol scale. [b] Yield of products obtained from radial preparative-layer chromatography. [c] Product is a mixture of diastereomers.

Given the reactivity of sp^2-hybridized organolithiums, a wide range of substituents can be installed in yields ranging from good to excellent. A C-5 carbomethoxy group was established on quenching with excess methyl chloroformate (entry 1). Heteroatoms and acyl groups (entries 2−5, 7, and 8) were implemented on treatment with the appropriate electrophiles. Reaction of anion **11** with benzaldehyde (entry 6) resulted in **13f** as a mixture of diastereomers. Relatively unreactive electrophiles such as iodoethane gave a good yield of the ethyl-substituted dihydropyridone. As a general trend, times required for hydrolysis from **11** to **13** lengthened according to the strength of the electron-withdrawing potential of the C-5 substituent.

Intrinsic to our design of selecting the Cl atom as a directing group was its dual ability to serve as a handle for substitution reactions. In this system, the chlorine atom is a proficient enabling element for substitution under a variety of reaction conditions. Substitution of nucleophilic reagents can proceed through a Michael addition with concomitant expulsion of chloride to give the appropriately substituted products (Scheme 4). The addition of NaOMe in methanol

Scheme 4



providing the C-6 methoxy derivative **14** and the alkyation at C-6 with a lower ordered cyanocuprate yielding **15** both fall under this mechanistic domain.

Alternatively, substitution at C-6 can also be achieved through the use of Pd(0) catalysis. Our initial screening of several coupling reactions with $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Pd(dppf)_2$ was met with no success as these catalysts all resulted in recovery of the starting material. We then employed conditions reported by Fu, utilizing $Pd(Pt\text{-}Bu_3)_2$, which proved to be highly effective in this system.[11] A Negishi coupling using phenylzinc chloride gave **16**, and a Stille coupling reaction with vinyltributylstannane rendered **17** under the auspices of this catalyst. The highly functionalized heterocycles shown in Scheme 4 are achieved in good yields and with exclusive control of regiochemistry in four synthetic steps.

(10) For a contemporary mechanistic discussion on directed lithiations relating to kinetic versus thermodynamic arguments, see: Gros, P.; Choppin, S.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2243.

(11) Littke, A. F.; Scjwarz, Z. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

In summary, we have disclosed a new route for the preparation of highly functionalized and diversified 2,3-dihydro-4-pyridones. The methodology uses sequential lithiations: first at C-6 and then at C-5 of 1,2-dihydropyridines as a means toward these dihydropyridones. The selection of chlorine as a substituent at the C-6 position facilitates the second lithiation event at C-5 with concomitant trapping of electrophiles. Finally, the chloride additionally allows for the substitution of a range of groups at C-6. Extension of this methodology toward other heterocycles and natural products of interest is currently underway and will be reported in due course.

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM 34442). D.Y. would also like to thank the NIH for a research training supplemental Minority Graduate Research Assistantship.

Note Added after ASAP Publication. Compounds **16** and **17** were incorrectly labeled in the paragraph below Scheme 4 in the version published ASAP November 8, 2005; the corrected version was published ASAP November 8, 2005.

Supporting Information Available: General experimental procedure for **13**, experimental procedures for **10** and **14**−**17**, and spectroscopic characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052313A