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Partial Reduction of Pyridinium Salts as a Versatile Route to Dihydropyridones

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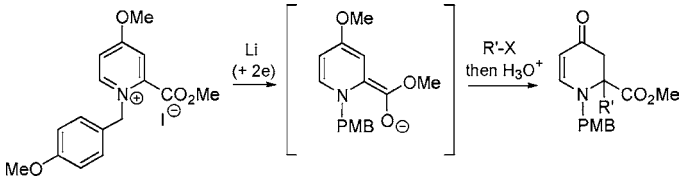
ABSTRACT

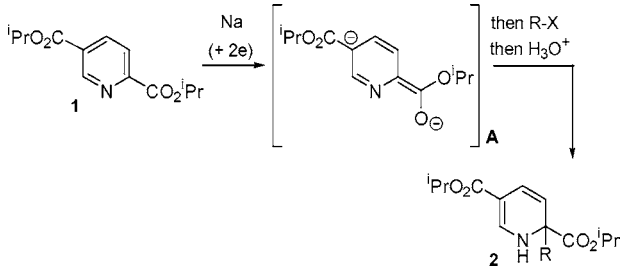


The addition of two electrons to a pyridinium salt turns it into a nucleophile. The intermediate generated by the reduction of such salts can be reacted successfully with a range of different electrophiles (acids, alkyl halides, and carbonyl compounds) and the intermediate hydrolyzed in situ to provide a wide range of dihydropyridones. Each position on the dihydropyridone ring is then accessible using standard synthetic manipulations.

We have recently reported the application of dissolving metal/ammonia reductions (Birch reduction) to disubstituted pyridines; this is a useful reaction sequence because it produces heterocyclic structures with potential uses in natural product synthesis and medicinal chemistry.[1] For this reduction to proceed effectively it was found that double activation of the pyridine nucleus, with two electron-withdrawing groups, was required. Moreover, the correct substitution pattern of these electron-withdrawing groups around the ring was crucial to stabilize intermediate dianions generated by the addition of two electrons (see **A**, Scheme 1).[1,2] If these two requirements were not met, the reduction failed.[2] While this methodology was robust and compatible with a wide range of electrophiles, it was discovered that the scope for modification of the products thus generated was limited. This problem has its origins in the fixed carbon substitution pattern that two electron-withdrawing groups imposes.

In an effort to create a more general approach to pyridine reduction, an alternative means of activating the pyridine

Scheme 1[a]



[a] Conditions: Na, NH_3, then R-X (yields 78−100%).

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(1) Donohoe, T. J.; McRiner, A. J.; Sheldrake, P. *Org. Lett.* **2000**, *2*, 3861. Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435. Donohoe, T. J.; Mace, L. H.; Helliwell, M.; Ichihara, O. *Synlett* **2002**, 331.

(2) Donohoe, T. J.; Compton, R. G.; Johnson, D. J.; Wadhawan, J. D. *Tetrahedron* **2004**, *60*, 5945.

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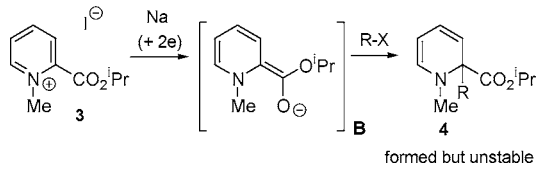
nucleus was sought. The use of pyridinium salts as activated electrophilic substrates for reduction via the use of organometallic reagents and hydride donors has been well documented in the literature.[3] It was believed that activation of the nitrogen would afford substrates viable for reduction. Initial investigation of this area showed promise with the formation and reduction of **3** (Scheme 2). However, the

Scheme 2[a]



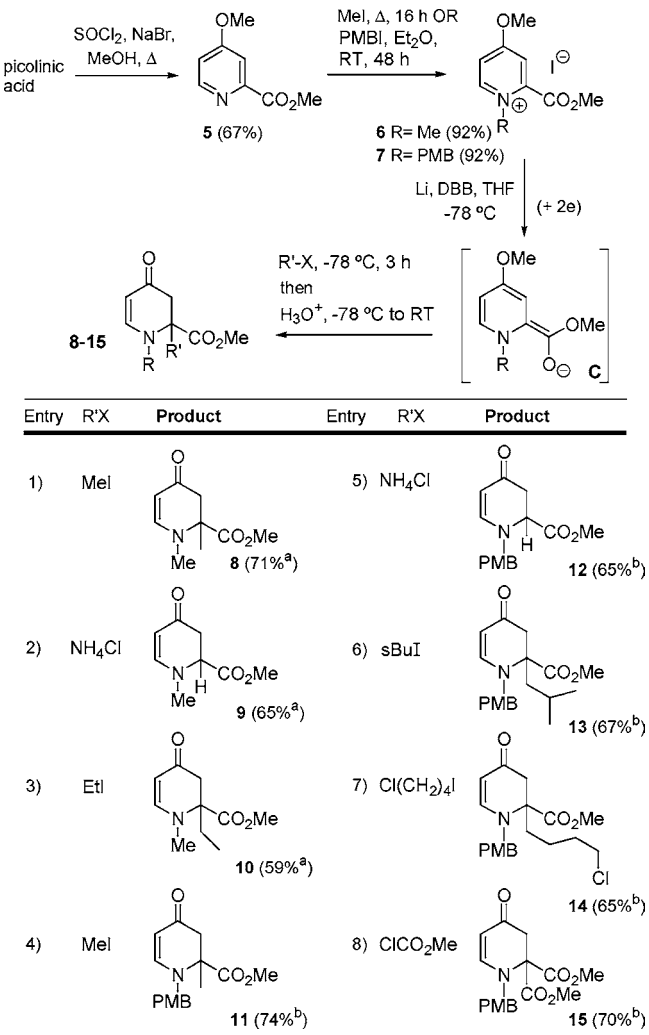
[a] Conditions: Na, NH_3, then R-X.

yields of dihydropyridine **4** were poor; the product degraded rapidly precluding effective purification. These observations are consistent with other reports of the instability of 1,2-dihydropyridines in the literature and our attempts to trap the reduced product via a Diels Alder reaction met with limited success.[4] Therefore, a method of stabilizing the dihydropyridine product was required.

At this point we were inspired by the work of Comins regarding Grignard addition to C-4 methoxy-substituted acylpyridinium salts.[5] We undertook an efficient, one-pot, synthesis of activated pyridine **5** from picolinic acid (Scheme 3).[6] Subsequent N-alkylation was achieved in excellent yield to furnish pyridinium salts **6**[7] and **7**. The rationale behind the addition of a methoxy group at C-4 was to avoid the generation of an unstable 1,2-dihydropyridine after reduction: acid-catalyzed hydrolysis in situ was predicted to liberate a dihydropyridone that would be straightforward to handle. As our strategy involved the use of an aqueous acid quench to achieve the hydrolysis, this sequence was incompatible with ammonia solvent. Thus, we switched to a reduction protocol developed over the past few years, using lithium and di-*tert*-butylbiphenyl (DBB) or sodium and naphthalene as a source of electrons (ammonia-free conditions).[8]

Initial investigations focused on the reduction of the *N*-methyl pyridinium salt **6**. The reduction/hydrolysis strategy

Scheme 3[a]



[a] Conditions: [a] Na, naphthalene; [b] Li, DBB.

proved very effective, with isolation of the desired dihydropyridone being achieved in an efficient manner (entry 1−3, Scheme 3). The instability that had plagued the previous products was completely absent. The reduction protocol was then applied to pyridinium salt **7**, so that more versatile *N*-protecting groups could be taken through the reduction/hydrolysis sequence. The dihydropyridones (**11**−**14**) were furnished in good yield using a range of electrophiles. We were pleased to find that the methodology was applicable to electrophiles, such as methyl chloroformate, that cannot be used under the standard Birch reduction conditions (entry 8, Scheme 3).[7] Thus we have defined a highly versatile method for introducing groups α to the nitrogen with great potential for broader synthetic application.

Next, we progressed on to elaboration of the template generated by this methodology, demonstrating that functionality can be introduced at any position around the dihydropyridone ring (Scheme 4). The chemistry of dihydropyridones is well documented in the literature[9] and we aimed to use a variety of precedented transformations to illustrate the potential for derivatization.

(3) Thiessen, L. M.; Lepoivre, J. A.; Alderweireldt, F. C. *Tetrahedron Lett.* **1974**, *15*, 59. Francis, R. F.; Davis, W.; Wiesner, J. T. *J. Org. Chem.* **1974**, *39*, 9, 59. O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201. Zhao, G.; Deo, U. C.; Ganem, B. *Organic Lett.* **2001**, *3*, 201. For a general review see: Keay, J. G. In *Compehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; p 579.

(4) Kunng, F.-A.; Gu, J.-M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262.

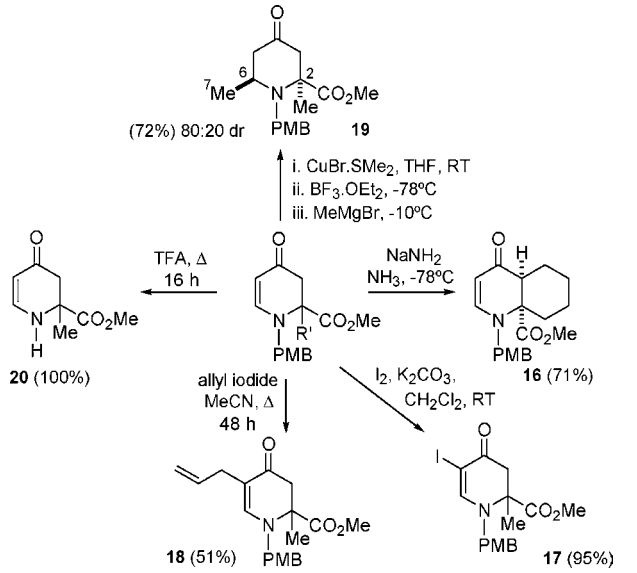
(5) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. For recent references, see: Comins, D. L.; Killpack, M. O.; Despagnet, E.; Zeller, E. *Heterocycles* **2002**, *58*, 505. Kuethe, J. T.; Comins, D. L.; *J. Org. Chem.* **2004**, *69*, 5219.

(6) Sundberg, R. J.; Jiang, S. *Org. Prep. Proced. Int.* **1997**, *29*, 117. Acyl pyridinium salts of **5** were not suitable substrates for reduction.

(7) Essawi, M. Y.; Portoghese, P. S. *J. Heterocycl. Chem.* **1983**, *20*, 477.

(8) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1327. Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015.

Scheme 4



The C-3 position was accessible using enolate chemistry. Reaction of dihydropyridone **14** with base[9] ($NaNH_2$) allowed an intramolecular displacement reaction; the cyclized product **16** was isolated as a single diastereomer, proven to have *cis* ring fusion by X-ray crystallography.[10]

Functionalization of the C-5 position was achieved by taking advantage of its position β to the nitrogen, and its consequent enamine character. Reaction of **11** with molecular iodine yielded the desired C-5 halo dihydropyridone **17** in excellent yield.[11] This versatile intermediate now presents many opportunities for derivatization including radical chemistry and metal-catalyzed coupling reactions. In addition, the C-5 position could also be derivatized by reaction of the enamine (**11**) with allyl iodide,[12] providing **18** in acceptable yield.

The C-6 position proved modifiable through conjugate addition methodology. Utilizing methodology reported by Comins et al.,[13] the reaction of **11** with methylmagnesium bromide, copper(I) bromide and boron trifluoride diethyl etherate afforded the conjugate addition product **19** (Scheme 4). This reaction gave a diastereomeric ratio of 80:20, with the stereochemistry of the major diastereoisomer identified via NOE experiments.[14] This control of relative stereochemistry at the C-6 carbon is promising for future synthetic studies.

The *N*-methyl-protected dihydropyridones (e.g., **8**) were not viable as substrates for elaboration of the ring nitrogen. Attempts to remove the *N*-Me group under electrophilic, nucleophilic or oxidative conditions returned starting material or led to decomposition. However, the PMB-protected class of compounds, e.g. **11**, proved highly versatile. Thus, treatment of **11** with trifluoroacetic acid led to formation of the deprotected dihydropyridone **20** in quantitative yield. Deprotection of the nitrogen creates the potential for *N*-substitution with many other functional groups and provides a starting point for future syntheses.

In conclusion, we have reported a concise route to important synthetic building blocks starting from a cheap and readily available starting material. It has also been shown that these molecules can be derivatized at every position around the ring, enhancing their utility to organic chemists. This chemistry provides dihydropyridones via a process that generates *nucleophilic* heterocyclic intermediates; as such it is complementary to known methodologies that harness the electrophilic nature of pyridinium salts.

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Supporting Information Available: ^1H NMR spectra and spectroscopic data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For reviews see: Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491. Joseph, S. P.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870.

(10) X-ray crystallography by Dr A. Cowley, University of Oxford.

(11) Sugiyama, N.; Yamamoto, M.; Hashima, C. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2690. Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141.

(12) Meyers, A. I.; Elworthy, T. R. *J. Org. Chem.* **1992**, *57*, 4732.

(13) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. See also: Liu, J. F.; Heathcock, C. H.; *J. Org. Chem.* **1999**, *64*, 8263. Weymann, M.; Schultz-Kukula, M.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 7835.

(14) The NOE experiments were performed on the major diastereoisomer of **19**. Irradiation of the C-7 methyl group showed a strong enhancement to the proton attached to C-6 but no enhancement of the methyl group attached to C-2. However, irradiation of the C-2 methyl group showed a strong enhancement to the proton on C-6. Finally, irradiation of the C-6 proton showed strong enhancement to both methyl groups at C-2 and C-7.