ORGANIC LETTERS

2009
Vol. 11, No. 23
5562−5565

Regioselective Nucleophilic Addition to Pyridinium Salts: A New Route to Substituted Dihydropyridones

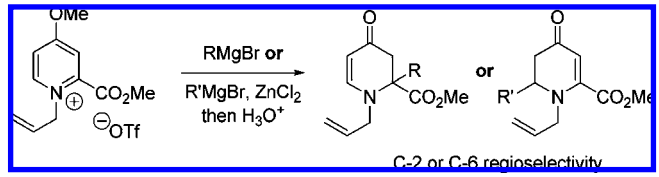
Timothy J. Donohoe,*,† Matthew J. Connolly,† and Lesley Walton‡

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K. and Lilly Research Centre, Eli Lilly and Company, Ltd., Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, U.K.

timothy.donohoe@chem.ox.ac.uk

Received October 19, 2009

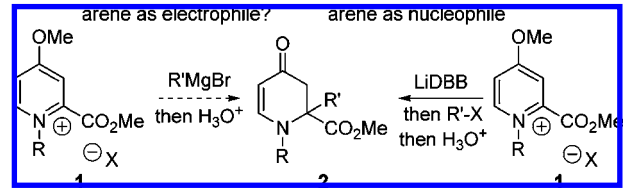
ABSTRACT



The regioselective addition of nucleophiles to pyridinium salts generates an intermediate enol-ether, which can be hydrolyzed *in situ* to provide a range of dihydropyridones. Certain Grignards have shown inherent differences in the regioselectivity of addition to these salts, and this difference can be tuned to give single regioisomeric addition products. The dihydropyridone products can be further manipulated in many ways using standard transformations.

We have previously reported on the ammonia-free Birch reduction of substituted pyridinium salts **1** (Scheme 1).[1] Addition of two electrons to the aromatic system gives an anionic intermediate that is capable of reaction with electrophiles. After *in situ* hydrolysis, the resultant dihydropyridones **2** that are formed have potential applications in natural product synthesis and medicinal chemistry.[2] However, during the Birch reduction problems have been encountered concerning the reproducibility of some results with pyridinium salts. In particular, the low solubility of salts such as **1** can lead to variable results and has hampered attempts to scale up the reduction.

Scheme 1



Recently, it has been demonstrated that similar unsubstituted dihydropyridones are accessible *via* nucleophilic addition to 4-methoxy substituted pyridinium salts.[3−6] Encouraged by these results, we proposed that addition of Grignard reagents to pyridinium salts such as **1**, followed by acidic

† University of Oxford.
‡ Eli Lilly and Company, Ltd.

(1) (a) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435. (b) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Thomas, R. E.; Chiu, J. Y. K.; Rodrigues, J. S.; Compton, R. G.; Banks, C. E.; Tomcik, P.; Bamford, M. J.; Ichihara, O. *Org. Biomol. Chem.* **2006**, *4*, 1071.

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

(3) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.

(4) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985.

(5) Knapp, S.; Yang, C.; Pabbaraja, S.; Rempel, B.; Reid, S.; Withers, S. G. *J. Org. Chem.* **2005**, *70*, 7715.

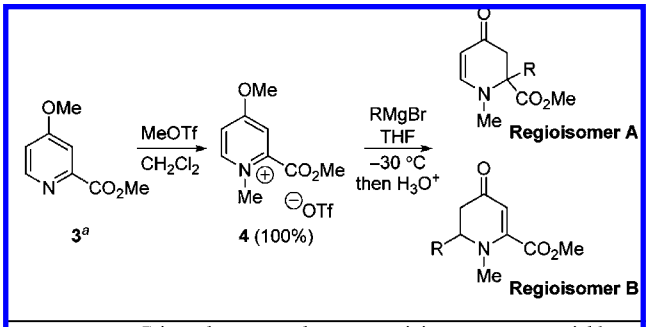
(6) Ege, M.; Wanner, K. T. *Org. Lett.* **2004**, *6*, 3553.

10.1021/ol902402v CCC: $40.75
Published on Web 11/05/2009

hydrolysis, could provide a useful alternative to the Birch reduction, but this time using the aromatic heterocycle as an electrophile.

Our efforts began with the THF-soluble pyridinium salt **4**, which was prepared in quantitative yield from the known disubstituted pyridine **3** and methyl triflate (Scheme 2).[7]

Scheme 2



entry	Grignard	product	regioisomer	yield
1	MeMgBr	5	A	89%
2	EtMgBr	6	A	97%
3	^{n}HexMgBr	7	A	92%
4	^{i}BuMgBr	8	A	91%
5		9	B	69%
6		10	B	60%

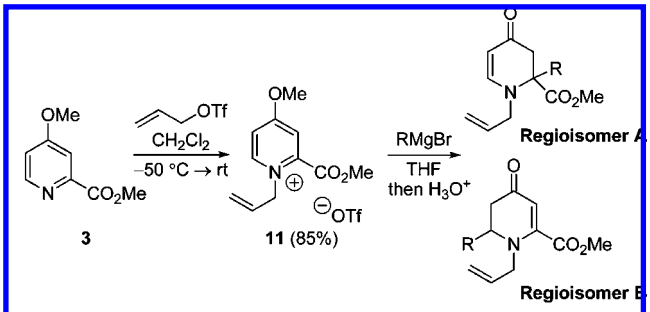
[a] Compound **3** was prepared in one step from commercially available picolinic acid.

Pleasingly, treatment of **4** with methylmagnesium bromide, followed by *in situ* hydrolysis, gave dihydropyridone **5** as a single regioisomer in 89% yield. This is a rare example of nucleophilic addition to a C-2 substituted pyridinium salt, generating a tertiary center with complete control of regioselectivity.[8] With this success in hand, dihydropyridones **6**−**10** were prepared in excellent yield from their corresponding Grignard reagent.

Interestingly, we found that alkenyl and alkynyl Grignards gave another regioisomeric product, resulting from nucleophilic attack at C-6 rather than attack at C-2, as observed for alkyl Grignards (Scheme 2, entries 5 and 6). We attributed this discrepancy to the fact that harder nucleophiles would tend to attack at the harder (more electron-deficient) C-2 center, adjacent to the electron-withdrawing ester group, and softer nucleophiles would attack the softer C-6 center.[9] The importance of hard and soft factors in additions to pyridinium salts has previously been described by Yamaguchi et al.[10]

We were disappointed to find that attempts at N-demethylation of the dihydropyridones **5**−**8**, under nucleophilic, electrophilic, or oxidative conditions, resulted in either recovery of starting material or decomposition. This limitation would impose a significant barrier on the synthetic utility of this methodology, so we decided to investigate an alternate N-protecting group. Corey has demonstrated that reaction of substituted pyridines with allyl triflate (generated *in situ* from allyl alcohol, triflic anhydride, and a tertiary amine base) produces N-allyl pyridinium salts in good yield.[11] Application of Corey's protocol to pyridine **3** furnished pyridinium salt **11** in excellent yield, and treatment of **11** with methylmagnesium bromide furnished dihydropyridone **12** in 74% yield (Scheme 3). It was subsequently found that

Scheme 3



entry	Grignard	temperature	product	isomer	yield
1	MeMgBr	−30 °C	12	A	74%
2	MeMgBr	−60 °C	12	A	86%
3	MeMgBr	−60 °C	12	A	84%[a]
4	EtMgBr	−60 °C	13	A	89%
5	^{n}HexMgBr	−60 °C	14	A	86%
6	^{i}PrMgCl	−60 °C	15	A	76%
7	^{t}BuMgCl	−60 °C	16	A	50%
8	PhMgBr	−60 °C	17	A	35%
			18	& B	36%
9		−60 °C	19	A	45%
			20	& B	44%

[a] Reaction performed on a 2.5 g (7 mmol) scale.

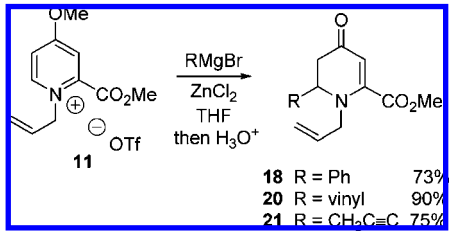
conducting the Grignard addition at −60 °C improved the yield of **12** to 86% and, pleasingly, performing the addition on a 2.5 g scale did not result in any significant reduction in yield, scale-up difficulties being a major limitation of Birch reduction methodology with these substrates. Other alkyl Grignards gave their corresponding dihydropyridones in similarly excellent yield. While we found that the yield of dihydropyridone was reduced as the bulk of the Grignard reagent was increased, note that dihydropyridones **15** and **16** could not be prepared by the Birch reduction route owing to the poor S_N2 substitution reactions of the corresponding secondary and tertiary bromide electrophiles. The synthesis of dihydropyridones **15** and **16** highlights the greater versatility of this methodology over the Birch reduction (Scheme 3, entries 6 and 7). Unfortunately, addition of aryl and vinyl

(7) Sundberg, R. J.; Jiang, S. *Org. Prep. Proced. Int.* **1997**, *29*, 117.
(8) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398.
(9) (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (b) Keinan, E.; Roth, Z. *J. Org. Chem.* **1983**, *48*, 1769.
(10) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215.
(11) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675.

Grignard reagents gave essentially 1:1 mixtures of regioisomers, which was disappointing given that addition to N-methyl salt **4** furnished only the C-6 addition products (entries 8 and 9). The reason for this is at present unclear, but it is possible that the N-allyl group adopts a conformation that hinders the C-6 position more than a simple Me group and so reduces the rate of nucleophilic attack at that center.

With 1:1 regioisomeric mixtures being of little synthetic utility, we naturally decided to improve the selectivity of addition to an acceptable level. Building on our hypothesis that harder nucleophiles add to the C-2 position and softer nucleophiles add to the C-6 position, we prepared an organozinc species by *in siu* treatment of the Grignard reagent with zinc chloride prior to addition of the pyridinium salt **11**, hoping that this softer nucleophile would selectively add at C-6.[12] To our delight, the only regioisomer observed from this protocol was that resulting from C-6 addition, and these dihydropyridones were obtained in excellent yield (Scheme 4). Interestingly, reaction of **11** with ethylmagnesium bromide and zinc chloride gave the C-2 addition product as a single regioisomer in yield similar to that obtained in the absence of zinc chloride.

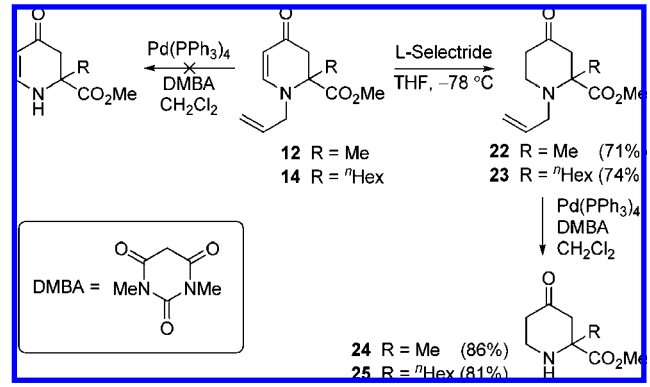
Scheme 4



[a] Treatment of **11** with EtMgBr under these conditions gave C-2 addition product **13** in 88% yield.

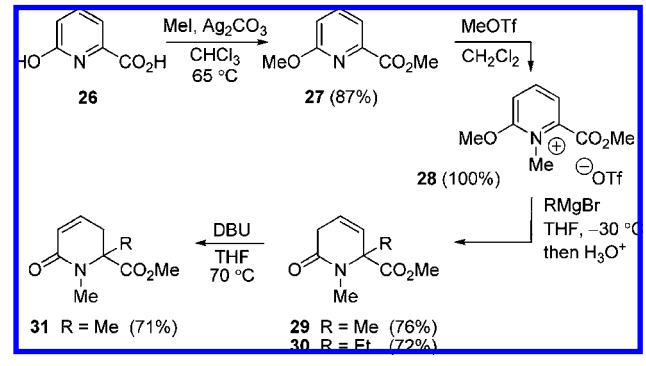
To allow elaboration of the ring nitrogen, we focused our efforts on the removal of the N-allyl group. Inspired by the work of Guibé on the palladium-catalyzed deallylation of amines, facilitated by 1,3-dimethylbarbituric acid,[13] we began by subjecting dihydropyridone **12** to Guibé's conditions. Unfortunately, only returned starting material was obtained from the reaction mixture. We reasoned that the ring nitrogen formed part of a vinylogous amide system and its basicity would be reduced to the extent that protonation by 1,3-dimethylbarbituric acid (pK_a (H_2O) = 4.7) would not occur. Conversion of the vinylogous amide to a tertiary amine would be likely to form part of any further synthetic manipulations on these products, so carrying out this transformation prior to N-deallylation would not pose any significant problems and would increase the basicity of the nitrogen, circumventing the aforementioned problem. Reduction of **12** and **14** with L-Selectride proceeded smoothly to provide piperidones **22** and **23**, and gratifyingly, treatment of these with Guibé's conditions furnished the deprotected products in excellent yield. This success creates the potential for N-functionalization with a range of electrophiles and provides a starting point for future synthetic work (Scheme 5).

Scheme 5



Having developed this simple and efficient procedure, we began to investigate whether it could be applied to other classes of substituted pyridinium salts that did not perform well under Birch reduction conditions. We have previously reported the ammonia-free Birch reduction of pyridinium salt **28**, prepared in excellent yield over two steps from commercially available 6-hydroxypicolinic acid **26**.[1b] Unfortunately, the yield of dihydropyridone **29** was modest under partial reducing conditions, thus prohibiting any synthetic application of this work. However, when pyridinium salt **28** was treated to the new nucleophilic conditions reported herein, we were delighted to find that the corresponding dihydropyridones could be easily isolated in good yield (Scheme 6). The olefin functionality in the product dihydropyridones was found to lie exclusively out of conjugation with the carbonyl group; however, we subsequently found that treatment with DBU in refluxing THF afforded the α,β-unsaturated dihydropyridones in good yield.

Scheme 6



In conclusion, we have developed an efficient and practically simple alternative to the Birch reduction of pyridinium

(12) For examples of organozinc reagents behaving as soft nucleophiles, see: (a) Dieter, R. K.; Guo, F. *J. Org. Chem.* **2009**, *74*, 3843. (b) Komanduri, V.; Pedraza, F.; Krische, M. *J. Adv. Synth. Catal.* **2008**, *350*, 1569.

(13) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.

salts. Nucleophilic addition to 4-methoxy substituted salts such as **11** yielded a range of dihydropyridones, after *in situ* hydrolysis, with the potential for the introduction of a variety of groups at the C-2 or C-6 position. We have demonstrated the smooth deallylation of the product dihydropyridones, enabling further N-functionalization and highlighting the synthetic utility of this methodology. Furthermore, the nucleophilic addition to regioisomeric pyridinium salt **28** is reported allowing access to the corresponding dihydropyridones. The overall yield of dihydropyridone has been improved for both salts by using this methodology, compared to Birch reduction.

Acknowledgment. We thank the EPSRC and Eli Lilly and Company Ltd. for funding this project.

Supporting Information Available: Full experimental details as well as ^{1}H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902402V