Practical and Highly Regio- and Stereoselective Synthesis of 2-Substituted Dihydropyridines and Piperidines: Application to the Synthesis of (−)-Coniine

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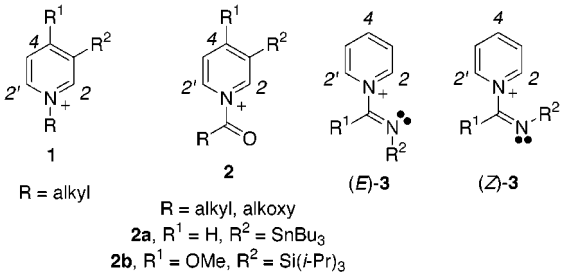
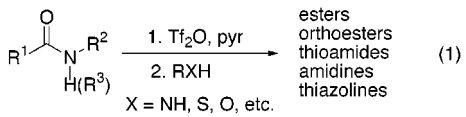
The piperidine subunit is one of the most important pharmacophores that is widely found in biologically active molecules and natural products. Many synthetic methodologies have been developed to access these very useful heterocyclic compounds.[1] One very attractive and cost-effective approach consists of activating pyridine to generate either an *N*-alkyl- or an *N*-acylpyridinium salt **1** or **2** (R^1 and R^2 = H). A subsequent nucleophilic attack by an organometallic reagent generates a substituted dihydropyridine which can then be further derivatized.[2] The drawback of this approach is the lack of regiocontrol when an unsubstituted pyridinium salt is used. Typically, mixtures of 1,2- and 1,4-adducts which had to be separated were obtained. To circumvent this problem, several systems in which directing or blocking groups had to be included (such as in **2a** and **2b**) to achieve high levels of regio- and stereocontrol were developed. In this communication, we report a novel highly regio- and stereoselective approach to 2-substituted dihydropyridines from *unsubstituted N*-pyridinium salts. This approach relies on the stereoselective formation of the (*E*)-isomer of *N*-pyridinium imidate **3** from the corresponding amide in which the nitrogen imidate lone pair is oriented in the proper position to direct the addition of an organometallic reagent at the 2 position.



We have recently reported that secondary or tertiary amides could be activated toward nucleophilic attack upon treatment with triflic anhydride (Tf_2O) and pyridine. A subsequent addition of several heteronucleophiles (ROH, RNH_2, H_2S, etc.) gave rise to a variety of useful functional group transformations (eq 1).[3]

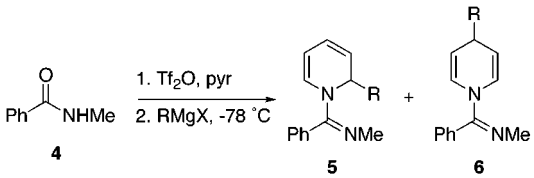


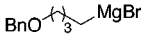
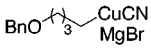
(1)

A spectroscopic investigation of the activation process has shown that *N*-pyridinium intermediate **3** was formed in the activation process.[4] NOESY experiments have confirmed that the (*E*)-imidate was formed as the only isomer when the appropriate R^1 and R^2 groups were selected. Initial studies on the activation of *N*-methylbenzamide, **4**, confirmed that the (*E*)-imidate was formed exclusively upon treatment with Tf_2O and pyridine.

The results of the addition of organometallic reagents are summarized in Table 1. As illustrated, the addition of organomagnesium reagents proceeds extremely well at low temperatures to give the desired 1,2-dihydropyridines, **5**, in good to excellent isolated yields. The regioselectivity of addition was found to be very high in general, favoring the 1,2-adduct in all cases. Although the addition of methylmagnesium bromide occurred with the exclusive formation of **5a** (entry 1), the addition of more hindered alkylmagnesium and functionalized Grignard reagents gave rise to slightly lower regioselectivities (entries 4,7). In those cases, it was found that the addition of the related cuprate reagents proceeded with slightly higher regioselectivities (entries 5,8). The regiochemical outcome with cuprates is in sharp contrast to what is observed with *N*-acylpyridinium salts which give exclusively 1,4-addition with these reagents.[5] The addition of phenyl-, vinyl-, and furyl Grignard proceeded extremely well to provide the 1,2-dihydropyridines in excellent yields.

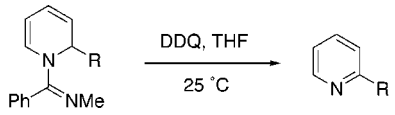
Table 1. Addition of Organomagnesium Reagents to Pyridinium Salts Derived from Amide **4**[6]



Entry	RMgX	5/6[a]	Yield (%)	Product
1	MeMgBr	>95/5	83	**5a**
2	PhMgBr	>95/5	84	**5b**
3		>95/5	86	**5c**
4	EtMgBr	90/10	82[b]	**5d**
5	EtCuCNMgBr	92/8	65	**5d**
6	2-FurylMgBr	>95/5	96	**5e**
7		90/10	70[c]	**5f**
8		94/6	76	**5f**

[a] Ratios determined by ^{1}H NMR. [b] Combined yield of dihydropyridines. [c] Organomagnesium reagent added at −30 °C.

To illustrate the synthetic utility of the 1,2-dihydropyridine adducts, compounds **5b** and **5f** were oxidized upon treatment with DDQ to afford the corresponding 2-substituted pyridines **7b** and **7f** in excellent yields (100 and 85% respectively) (eq 2).



(2)

Having established that the imidate lone pair could effectively direct the nucleophilic attack at the C-2, we then focused our

(1) For recent reviews on the stereoselective synthesis of piperidines, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862.

(2) From chiral *N*-alkylpyridinium salts, see; (a) Guilloteau-Berin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052. From chiral *N*-acylpyridinium salts, see: (c) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651. (d) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248. (e) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807. (f) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

(3) (a) Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677. (b) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908 and references therein.

(4) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**. In press.

(5) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315.

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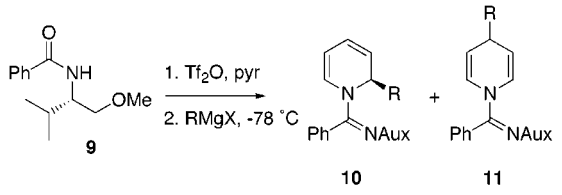
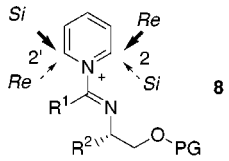
Table 2. Addition of Organomagnesium Reagents to Pyridinium Salts Derived from Chiral Amide **9**



entry	RM	10/11[a]	d.r.[a]	yield (%)	product
1	MeMgBr	>95/5	>95/5	77	**10a**
2	EtMgBr	75/25	>95/5	79[b]	**10b**
3	Et_2Zn	>95/5	>95/5	73[c]	**10b**
4	PhMgBr	90/10	>95/5	74	**10c**
5	PhMgBr[c,d]	>95/5	>95/5	89	**10c**
6	2-FurylMgBr	>95/5	>95/5	68	**10d**
7	1-HexynylMgBr	>95/5	>95/5	65	**12**

[a] Ratios determined by ^{1}H NMR. [b] Combined yield of dihydropyridines. [c] Added at −20 °C. [d] Prepared from PhLi.

attention to generation of enantiomerically enriched 2-substituted piperidines. The stereoselective addition to unsubstituted pyridinium salts is complicated by the fact that four electrophilic faces (2- and 2′-position, **8**) could be subjected to nucleophilic attack. If, however, a bulky substituent is introduced at the R^1 position, nucleophilic attack at the 2′-position (in **8**) may be suppressed. Neither this substituent nor the *N*-substituent of the imidate should preclude (*E*)-imidate formation. After extensive optimization, it was found that the optimal R^1 group was phenyl and that a bidentate chiral auxiliary derived from valinol produced excellent results in nucleophilic addition reactions.

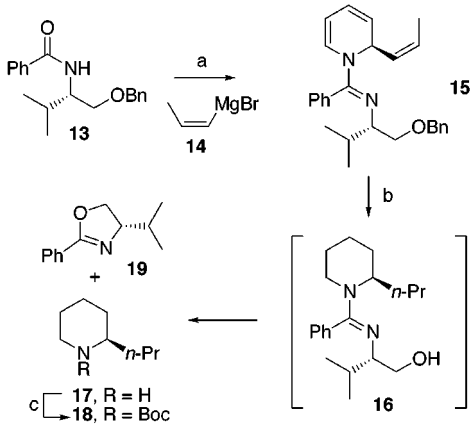


8

As shown in Table 2, amide **9** derived from (*S*)-valinol, in which the alcohol was protected as a methyl ether,[7] gave in most cases excellent regio- and diastereoselectivities.

Once again, although the addition of methylmagnesium bromide proceeded very well to afford **10a**, the addition of more hindered alkylmagnesium reagents suffers from a lack of regiocontrol (compare entries 1 and 2). For the introduction of alkyl chains, we found that although organocuprates led to slightly better regioselectivities, the diastereoselectivies were quite modest. In contrast, addition of diethylzinc proceeded extremely well to produce **10b** in excellent yield, regio- and diastereoselectivities

Scheme 1. Synthesis of (*R*)-(−)-Coniine **17**[a]



[a] Conditions: (a) i) Pyridine, Tf_2O, CH_2Cl_2, −40 to 0 °C ii) **14**, −78 to −30 °C, 61%; (b) H_2, $Pd(OH)_2$, EtOH, 25 °C then add cyclohexene and AcOH, 100 °C; (c) $(Boc)_2O$, THF, NaOH 2.0 M, 60% (two steps).

(entry 3). The addition of aryl-, furyl- and alkynylmagnesium bromides led to the adducts with excellent regio- and stereocontrol (entries 4−7).[8] To further demonstrate the synthetic potential of this methodology, an expedient synthesis of the piperidine alkaloid (*R*)-(−)-coniine starting from amide **13** is presented (Scheme 1).[9] The addition of *cis*-1-propenylmagnesium bromide **14** proceeded well to yield 1,2-dihydropyridine **15** in 61% isolated yield. Hydrogenation of the three alkenes and hydrogenolysis of the benzyl ether led to **16** which spontaneously cyclized under the reaction conditions to the oxazoline **19** and to (*R*)-(−)-coniine **17** which was isolated as its *N*-Boc derivative **18** in 60% yield for the two-step process.[10]

In summary, we have reported an expedient regio- and stereoselective approach to 2-substituted dihydropyridines that relies on the powerful directing ability of the imidate group. Further applications of this methodology will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Typical procedure: A solution of **4** in CH_2Cl_2 containing pyridine (3.0 equiv) was cooled to −40 °C and treated with Tf_2O (1.2 equiv). The mixture was then warmed to room temperature. After 1 h of stirring at room temperature, the solution was cooled to −78 °C, and the nucleophile (2.5 equiv) was added. The reaction was stirred at −78 °C until TLC analysis showed complete disappearance of the starting amide (ca. 3 h). Aqueous workup, followed by chromatography, yielded the dihydropyridine. For further details, see Supporting Information.

(7) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

(8) The 1,2-dihydropyridine, **10e**, proved unstable and was isolated as the fully hydrogenated compound **12**.

(9) Coniine is a common synthetic target for testing new piperidine synthesis methodology. For selected examples, see; (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155. (b) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (c) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699. (d) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084.

(10) The stereochemistry of the chiral center created in **15** was established by comparing the optical rotation of **18** with the previously reported value ($[\alpha]^{23}_D = -29.9$ (*c* 0.67, $CHCl_3$); $[\alpha]^{23}_D$ lit. = −31.6 (*c* 0.86, $CHCl_3$): Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173.