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# Nucleophilic Addition to 3-Substituted Pyridinium Salts: Expedient Syntheses of (−)-L-733,061 and (−)-CP-99,994

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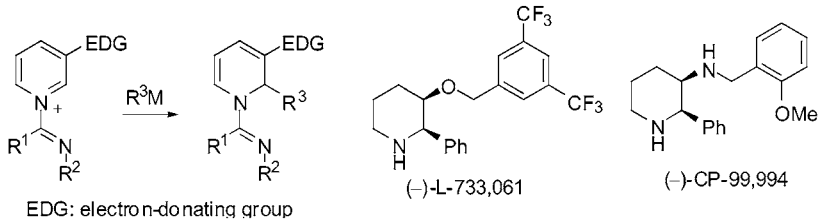
## ABSTRACT




**The addition of nucleophiles to 3-substituted pyridinium salts prepared from *N*-methylbenzamide and various pyridines has been investigated. Good to excellent regioselectivities favoring the 2,3-disubstituted 1,2-dihydropyridines were observed. The resulting 1,2-dihydropyridines led to the corresponding 2,3-disubstituted pyridines upon treatment with $Mn(OAc)_3/NaIO_4$. This methodology was also successfully applied to the enantioselective syntheses of (−)-L-733,061 and (−)-CP-99,994, two members of a new class of highly potent, nonpeptide, Substance P antagonists.**

Efficient syntheses of 2,3-disubstituted piperidines are becoming increasingly important since several studies have highlighted their unique biological activities.[1] For example, several Substance P antagonists such as L-733,060 (**1**) and CP-99,994 (**2**) contain this important pharmacophore unit (Figure 1).[2] Routes leading to enantiopure **1**[3] rely either on

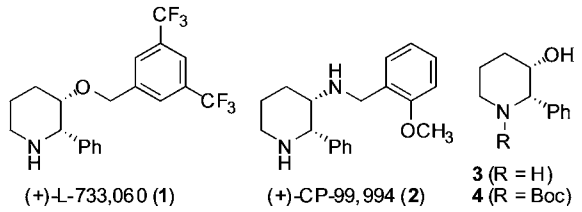



**Figure 1.** Structure of Substance P antagonists and precursors.

resolution techniques[4] or lengthy syntheses from a variety of chiral building blocks such as L-glutamic acid[5] and L-phenylglycine.[6] Efficient syntheses of piperidines **3** and **4**, valuable precursors for the synthesis of **1**, have also been reported.[7] Likewise, routes leading to enantioenriched **2**[8] include resolution of racemic intermediates[9] or linear syntheses starting from L-serine,[10] (*R*)-1-phenyl-1,2-ethanediol,[11]

(1) For recent reviews on the synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989.

(2) For a review on Substance P, see: Datar, P.; Srivastava, S.; Coutinho, E.; Govil, G. *Curr. Top. Med. Chem.* **2004**, *4*, 75−103.

(3) For a racemic route to **1**, see: Tomooka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc.* **2000**, *122*, 408−409.

(4) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545−2550.

(5) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927−1929.

(6) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915−917.

(7) (a) Bodas, M. S.; Upadhyay, P. K.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 987−988. (b) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223−6225. (c) Stadler, H.; Bös, M. *Heterocycles* **1999**, *51*, 1067−1071. (d) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099−7100.

(8) For a racemic route to **2**, see: Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831−5834.

(9) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911−4913.

(10) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071−5072.

(11) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979−7982.

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or L-glutamic acid.[2] A catalytic asymmetric approach to **2**, based on a nitro-Mannich reaction, has also been recently reported.[12]

Our research group has been involved in the development of new methodologies for the preparation of useful enantiopure piperidine-derived building blocks from cheap chemical commodities such as pyridine. A strategy that has been frequently used to prepare piperidine alkaloids involves the addition of a nucleophile to an *N*-alkyl- or an *N*-acylpyridinium salt such as **5** or **6**, as illustrated in Figure 2. We

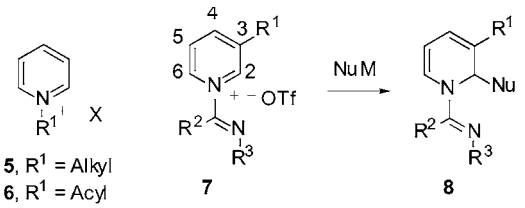


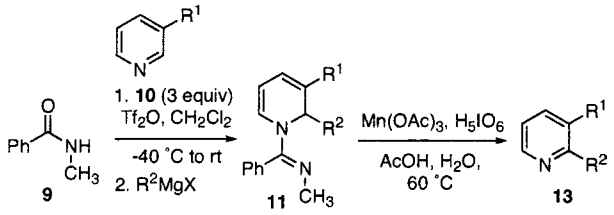

**Figure 2.** Pyridinium salts as precursors to dihydropyridines.

recently reported that the addition of nucleophiles to **7** ($R^1$ = H), a new class of pyridinium salts readily accessible from secondary amides,[13] proceeds with very high diastereo- and regiocontrol to produce dihydropyridines **8** ($R^1$ = H).[14,15]

To extend the scope of our methodology to access more substituted piperidines from cheap precursors, we investigated the addition of nucleophiles to 3-substituted pyridinium salts (**7**, $R^1 \neq$ H). Obviously, the addition can occur either at the C-2, C-4, or C-6 position to give potentially three regioisomeric dihydropyridines.[16] On the basis of both the strong directing effect of the imidate nitrogen and stereoelectronic effects,[16] we anticipated that high regiocontrol would be obtained and an expedient route to 2,3-disubstituted piperidines could be developed.[17]

The addition reactions of methyl- and phenylmagnesium bromide to the pyridinium salts derived from *N*-methylbenzamide and substituted pyridines **10a**−**d** (3 equiv) proceeded well to give predominantly, and in some cases exclusively, 2,3-disubstituted 1,2-dihydropyridines **11** (Table 1). Although

**Table 1.** Nucleophilic Addition to 3-Substituted Pyridinium Salts Derived from **9** and **10** and Oxidation to 2,3-Disubstituted Pyridines




| entry | $R^1$ | $R^2$ | **11**:**12**[a] | yield % (**11**)[b] | yield % (**13**) |
|---|---|---|---|---|---|
| 1 | Me (**10a**) | Me | 89:11 | 80 (**11a**) | 81 (**13a**) |
| 2 | Me (**10a**) | Ph | 79:21 | 72 (**11b**)[c] | 80 (**13b**) |
| 3 | OMe (**10b**) | Me | >95:5 | 100 (**11c**) | --- |
| 4 | OMe (**10b**) | Ph | >95:5 | 94 (**11d**) | 94 (**13d**) |
| 5 | Cl (**10c**) | Me | 95:5 | 85 (**11e**)[c] | 63 (**13e**) |
| 6 | Cl (**10c**) | Ph | 78:22 | 66 (**11f**)[d] | 91 (**13f**) |
| 7 | Br (**10d**) | Me | 92:8 | 80 (**11g**) | 57 (**13g**) |

[a] Ratio was determined by $^1$H NMR. [b] Isolated yield of **11**. [c] Combined yield of both isomers is 89%. [d] Combined yield of both isomers is 83%.

the addition reactions of methylmagnesium bromide provided ratios of products comparable to those observed with *N*-acylpyridinium salts,[17d] the addition of phenylmagnesium bromide proceeded in much higher regioselectivity.[18] The minor 2,5-isomer (**12**) occurred from nucleophilic addition at C-6, and we did not observe any product arising from attack at C-4.

To clearly establish the regiochemical outcome of these reactions, the major dihydropyridine adduct was oxidized to yield the corresponding 2,3-disubstituted pyridine. Much to our surprise, the oxidation turned out to be problematic. After extensive experimentation using a variety of oxidants, we found that the use of a substoichiometric amount of manganese triacetate and periodic acid as the terminal oxidant in acetic acid afforded pyridines **13** in good to excellent yields (Table 1).

With these encouraging results in hand, the diastereoselective version of the reaction was investigated in the context of the synthesis of the antipode of L-733,060 (**1**) and CP-99,994 (**2**) (Scheme 1). Deprotonation of 3-hydroxypyridine (**14**) with NaH in DMF, followed by addition of 3,5-bis(trifluoromethyl)benzyl bromide (**15**), afforded pyridine **16** in 70% yield.

Activation of amide **17**[19] in the presence of pyridine **16** (3 equiv) followed by the addition of phenylmagnesium bromide led to 1,2-dihydropyridine **18** in 84% yield and as a single regio- and diastereomer. The amount of pyridine

(12) Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276−277.

(13) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694−1703.

(14) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.

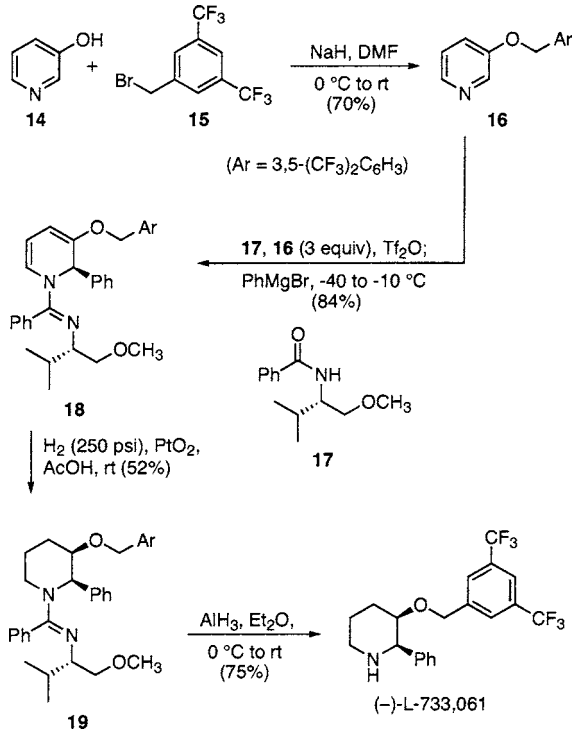
(15) For another example of a pyridinium salt giving 1,2,5,6-tetrahydropyridines in a highly regioselective process, see: Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360−6361.

(16) For a discussion of the factors responsible for the preferential formation of the 1,2-adduct over the 1,6-adduct, see: Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672−3679.

(17) For examples of addition of organomagnesium reagents to *N*-acyl 3-substituted pyridinium salts, see: (a) Chia, W.-L.; Shen, S.-W.; Lin, H.-C. *Tetrahedron Lett.* **2001**, *42*, 2177−2179. (b) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292−298. (c) Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1987**, *28*, 759−762. (d) Krow, G. R.; Cannon, K. C.; Carey, J. T. *J. Heterocycl. Chem.* **1985**, *22*, 131−135. (e) Comins, D. L.; Mantlo, N. B. *J. Heterocycl. Chem.* **1983**, *20*, 1239−1243. (f) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315−4319. (g) Lyle, R. E.; Marshall, J. L.; Comins, D. L. *Tetrahedron Lett.* **1977**, *18*, 1015−1018. For examples of addition of organotin reagents leading to 1,2-dihydropyridines, see: (h) Itoh, T.; Hasegawa, H.; Nagata, K.; Okada, M.; Ohsawa, A. *Tetrahedron* **1994**, *50*, 13089−13100. (i) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1988**, *53*, 3507−3512. (j) Yamaguchi, R.; Hata, E.-I.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1785−1788. (k) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287−288.

(18) For example, the addition of PhMgCl to *N*-acyl-3-picolinium salt (analogue to entry 2) gives a 16:66:15 mixture of C2:C6:C4 nucleophilic addition regioisomers (ref 17f).

**Scheme 1.** Synthesis of (−)-L-733,061




**16** could be reduced to 1.5 equiv if 2,6-di-*t*-butyl-4-methylpyridine was added as the proton scavenger. The yield dropped slightly to 70% using this procedure.[20] The diastereoselective hydrogenation of **18** from the opposite face of the phenyl ring at C-2 afforded piperidine **19** as a single diastereomer (>95:5) in 52% yield. Finally, alane reduction of the amidine yielded (−)-L-733,061 in 75% yield.

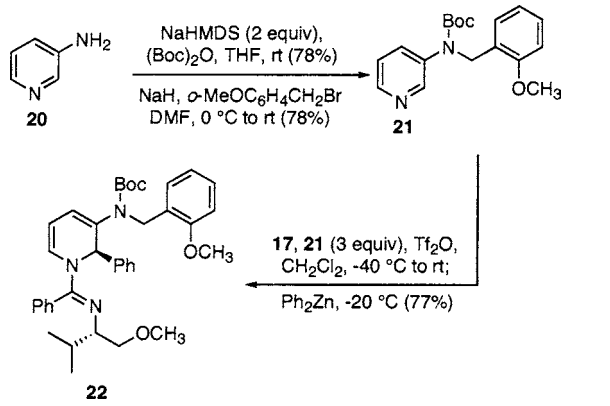
To further illustrate the potential of this methodology, we elected to prepare the antipode of CP-99,994 (**2**) by adding the appropriate organometallic reagent to the pyridinium salt derived from amide **17** and pyridine **21**. The presence of a much more sterically hindered group at C-3 may lower the regioselectivity of addition. The synthesis of pyridine **21** was straightforward, starting from 3-aminopyridine (**20**) (Scheme 2). Deprotonation of **20** with NaHMDS (2 equiv),[21] followed by addition of di-*tert*-butyl-dicarbonate, afforded a 78% yield of the mono-Boc-protected pyridine. Alkylation with *o*-methoxybenzyl bromide yielded pyridine **21** in 78% yield. As anticipated, the addition of various organometallic reagents to the pyridinium salt derived from amide **17** and pyridine **21** proved to be somewhat troublesome. Addition of PhLi and PhMgBr produced mixtures of dihydropyridines. However, we were pleased to see that the addition of $Ph_2Zn$ proceeded extremely well to give 1,2-dihydropyridine **22** in 77% yield. The hydrogenation of **22** proceeded uneventfully; however, the cleavage of the chiral auxiliary proved to be problematic.[22]

(19) For the preparation of amide **17** and its use in the stereoselective synthesis of 1,2-dihydropyridines, see ref 14.

(20) See Supporting Information for details.

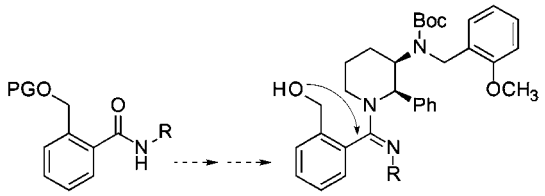
(21) Use of 1.1 equiv of NaHMDS resulted in the exclusive formation of the bis-Boc-protected pyridine in 42% yield (50% max yield); see Supporting Information.

**Scheme 2.** Preparation and Nucleophilic Addition to **21**



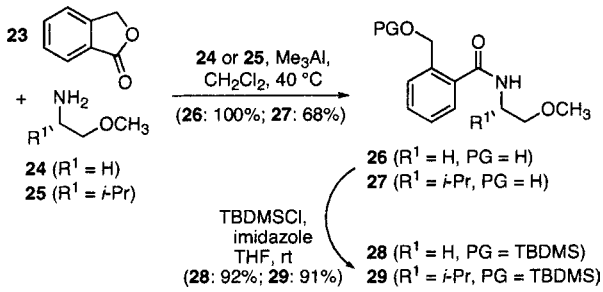

This unfortunate situation prompted us to devise a chiral amide with a latent hydroxy group on the aryl substituent to facilitate the hydrolysis of the amidine (Scheme 3).

**Scheme 3.** Hydroxy-Assisted Cleavage of the Auxiliary



TBDMS-protected amides **28** and **29** were easily prepared according to the sequence outlined in Scheme 4. Opening

**Scheme 4.** Synthesis of Novel Amides



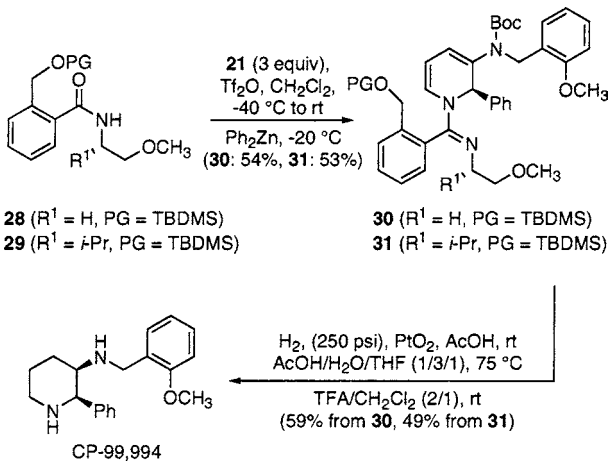

of phthalide (**23**) with 2-methoxyethylamine (**24**) using Weinreb's procedure afforded hydroxyamide **26**.[23] A slightly lower yield was obtained when *O*-methyl valinol (**25**) was used (68%), probably due to steric factors. Protection of the benzylic alcohol with TBDMSCl proceeded efficiently with both substrates to give amides **28** and **29** in excellent yields.

(22) Demethylation of the aromatic methyl ether occurred during the amidine reduction step.

(23) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4172.

The addition of $Ph_2Zn$ to the pyridinium salts derived from amides **28** or **29** and pyridine **21** produced the expected 1,2-dihydropyridines in 54 and 53% yields, respectively (Scheme 5). Hydrogenation of dienes **30** and **31** with $PtO_2$, followed by cleavage of the auxiliary under mildacidic conditionsand removal of the *N*-Boc protecting group with TFA, afforded (±)- and (−)-CP-99,994 (**2**), respectively.

**Scheme 5.** Synthesis of CP-99,994




In conclusion, we have shown that the addition of organometallic reagents to pyridinium salts substituted with an electron-donating group at the C-3 position gives predominantly the 1,2-dihydropyridine adducts. These can be readily oxidized to 2,3-disubstituted pyridines with manganese triacetate and periodic acid. Moreover, the resulting 1,2-dihydropyridines can be further used for the synthesis of 2,3-disubstituted piperidines. This was demonstrated by the concise syntheses of (−)-L-733,061 and (−)-CP-99,994. Further applications of this methodology will be reported in due course.

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**Supporting Information Available:** General information, experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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