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# Synthesis of 4-Substituted-1,4-Dihydropyridines

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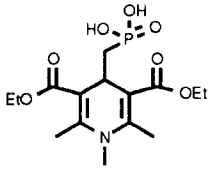
**Abstract:** A general synthesis of C-4-substituted dihydropyridines is described. The route exploits a standard Hantzsch ester synthesis followed by nucleophilic substitution of a halide with, for example, triethylphosphite. The resulting compounds could have interesting biological properties or may find use as haptens for preparing catalytic antibodies for hydride transfer reactions.

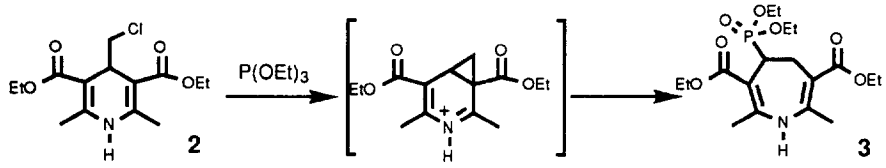

The dihydropyridine unit, first prepared by Hantzsch in 1882, is the principal structural component of several compounds with important pharmacological properties. These include calcium antagonists and platelet activating factors.[1] Recently, dihydropyridines containing taurine moieties were found to have aggregation and antioxidative properties.[2] Due to their therapeutic potential, considerable effort is consequently being devoted to the preparation of interesting new dihydropyridine derivatives. Here, the synthesis of compound **1** is reported *via* a versatile method that allows introduction of almost any nucleophilic group at the 4-position.



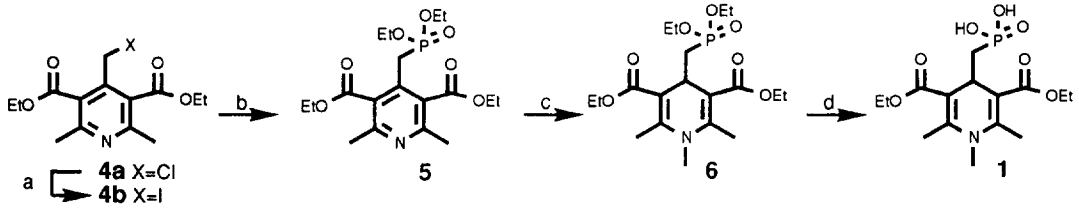

**1**

The chloromethyl dihydropyridine **2**, prepared by a standard Hantzsch ester synthesis,[3] was used as the starting material for the preparation of **1**. However, attempts to replace the halogen in **2** by direct

nucleophilic substitution with triethylphosphite were unsuccessful. The dihydroazepine **3** was obtained as the only product in these experiments, presumably due to formation of a cyclopropane intermediate as shown below.[4] For this reason, the corresponding pyridine derivative was prepared.




Oxidation of **2** with $HNO_3/H_2SO_4$[5] gave pyridine **4a**, which was converted to the iodide **4b** with NaI in acetone in 63% overall yield. Reaction of **4a** or **4b** with triethylphosphite at 130 °C subsequently produced the desired phosphonopyridine **5** in excellent yield (92%).[6] Treatment of compound **5** with dimethyl sulphate for 7 h at 65°C, followed by reduction of the resulting N-methylpyridinium monomethylsulphate with sodium dithionite, then yielded the phosphono-dihydropyridine **6** (46% over two steps).[7] The latter derivative was selectively hydrolyzed with bromotrimethylsilane in dichloromethane at room temperature to the phosphonic acid **1** (87%).[8,9]




a) NaI/dry acetone, r.t; 90%; b) $(EtO)_3P$/130 °C; 91%; c) i) $(MeO)_2SO_2$/65°C, 5 h , ii) $Na_2S_2O_4/NaHCO_3$/water, 1 h; 46%; d) TMSBr/dry $CH_2Cl_2$, 2 h, r.t.; 87%.

The synthetic scheme outlined above is likely to provide a general route to dihydropyridines containing polar functionality at C-4. Aside from their potential biological effects, compounds like **1** could conceivably be useful as haptens for producing antibodies that catalyze hydride transfer from a dihydropyridine to an aldehyde.[10] The phosphonate moiety, linked to a carrier protein via one of its oxygens, might mimic the carbonyl group undergoing reduction and the C-4 methylene group the in-flight hydride.[11] Despite much effort over the last decade,[12] relatively few catalytic antibodies have been reported for redox reactions and additional examples would be welcome.

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**References**

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1. a) Cooper, K.; Fray, M. J.; Parry, M. J.; Richardson, K.; Steele, J. *J. Med. Chem.* **1992**, 35, 3115. b) Alajarín, R.; Alvárez-Builla, J.; Vaquero, J. J.; Sunkel, C.; Fau de Casa-Juana, M.; Statkow, P. R.; Sanz-Aparicio, J. *Tetrahedron: Asymmetry* **1993**, 4, 617. c) Christiaans, J. A. M.; Windhorst, A. D.; Groenenberg, P. M.; van der Goot, H.; Timmerman, H. *Eur. J. Med. Chem.* **1993**, 28, 859. d) Review: Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 762.

2. Poikans, J.; Tirzitis, G.; Bisenieks, E.; Uldrikis, J.; Gurevich, V. S.; Mikhailova, I. A.; Duburs, G. *Eur. J. Med. Chem.* **1994**, 29, 325.

3. a) Brignell, P. J.; Bullock, E.; Eisner, U.; Gregory, E. B.; Johnson, A. W.; Williams, H. *J. Chem. Soc.* **1963**, 4819. b) Review: "Recent Advances in the Chemistry of Dihydropyridine", Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, 82, 223.

4. Gill, G. B.; Harper, D. J.; Johnson, A. W. *J. Chem. Soc.* **1968**, 1675. Compound **3**: $^1$H-NMR (300MHz, $CD_3OD$), δ: 1.12 (m, 6H); 1.19 (m, 6H); 2.22 (s, 3H); 2.27 (s, 3H); 2.33 (m, 1H); 3.50 (m, 1H); 3.95 (m, 4H); 4.09 (m, 1H); 4.16 (m, 4H), when DMSO-$d_6$ was used instead of $CD_3OD$, there was the signal 7.65 (s, 1H, NH).

5. Fox, H. H.; Lewis, J. I.; Wenner, W. *J. Chem. Soc.* **1951**, 1259. No 4-dealkylation product was obtained and attemps to use other oxidants, such as $NaNO_2$, failed.

6. Compound **4b**: mp (EtOH) = 71-73 °C. $^1$H-NMR (300MHz, $CDCl_3$), δ: 1.39 (t, J=7.1Hz, 6H); 2.29 (s, 2H); 2.51 (s, 6H); 4.44 (q, J=7.1Hz, 4H). MS ($FAB^+$): 392 ($M^+$+1, 100). Compound **5** : $^{31}$P-NMR: 24.6. $^1$H-NMR (300MHz, $CDCl_3$), δ: 1.25 (t, J=6.9Hz, 6H); 1.41 (t, J=7.1Hz, 6H); 2.58 (s, 6H); 3.68 (d, J=23.3Hz, 2H); 4.02 (m, 4H); 4.44 (q, J=7.1Hz, 4H). MS ($FAB^+$): 402 ($M^+$+1, 100).

7. a) for the methylation: Brook, P. R.; Karrer, P. *Justus Liebigs Ann. Chem.* **1957**, 605, 1. It is important to control the temperature to avoid side reactions since the pyridinium ring is very electrophilic. b) for similar

reductions, see: Traber, W.; Karrer, P. *Helv. Chim. Acta* **1958**, 41, 2067. Compound **6**: $^{31}$P-NMR: 29.8. $^{1}$H-NMR (300MHz, $CDCl_3$), δ: 1.30 (m, 12H); 1.71 (dd, J=6.5 and 17.3 Hz, 2H); 2.43 (s, 6H); 3.20 (s, 3H); 4.03 (m, 4H); 4.20 (q, J=6.8Hz, 4H); 4.39 (dt, J=6.5 and 14.6Hz, 1H). MS ($FAB^+$): 418 ($M^+$+1, 100).

8. Mckenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739. Compound **1**: mp (water)=145 °C. $^{31}$P-NMR: 25.4. $^{1}$H-NMR (500MHz, DMSO-$d_6$), δ: 1.25 (t, J=7.1Hz, 6H); 1.71 (dd, J=6.5 and 17.3Hz, 2H); 2.43 (s, 6H); 3.22 (s, 3H); 4.02 (q, J=6.5Hz, 1H); 4.23 (q, J=7.1Hz, 4H). MS ($FAB^+$): 494 ($M^+$+Cs, 30). $\varepsilon_{EtOH}^{340} = 4917\ M^{-1}\ cm^{-1}$.

9. All new compounds gave satisfactory analytical data.

10. There are several studies on the reducing capabilities of 1,4 dihydropyridines. a) Gelbard, G.; Lin, J.; Roques, N. *J. Org. Chem.* **1992**, 57, 1789. b) Baba, N.; Matsumura, Y.; Sugimoto, T. *Tetrahedron Lett.* **1978**, 4281. c) Kok, P. M. T.; Bastiaansen, L. A. M.; van Lier, P. M.; Vekemans, J. A. J. M.; Buck, H. M. *J. Org. Chem.* **1989**, 54, 1313. d) Berkous, R.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Bull. Soc. Chim. Fr.* **1994**, 131, 632. e) Pandit, U.K.; Mas Cabré, F.R.; Gase, R.A.; Nie-Sarink, M. *J. Chem. Soc., Chem. Commnun.* **1974**, 627. f) Review: Yasui, S.; Ohno, A. *Bioorganic Chemistry* **1986**, 14, 70.

11. a) Wu, Y-D.; Lai, D. K. W.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, 117, 4100. b) Wu, Y-D, Houk, K. N. *J. Am. Chem. Soc.* **1987**, 107, 2226. c) Review: Bunting, J. W. *Bioorg. Chem.* **1991**, 19, 456.

12. a) Hilvert, D. M. *Acc. Chem. Res.* **1993**, 26, 552. b) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, 252, 659.

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