Tetrahedron Letters, Vol. 33, No. 50, pp. 7635-7638, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

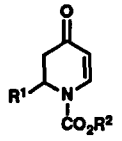
Conversion of *N*-Acyl-2,3-dihydro-4-pyridones to 4-Chloro-1,2-dihydropyridines using the Vilsmeier Reagent.

Rima S. Al-awar, Sajan P. Joseph and Daniel L. Comins*

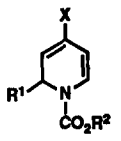
Department of Chemistry
North Carolina State University, Raleigh, NC 27695-8204

Abstract: *N-Acyl-2,3-dihydro-4-pyridones are converted to 1-acyl-4-chloro-1,2-dihydropyridines in one step using one equivalent of Vilsmeier reagent. This conversion was utilized in an asymmetric synthesis of (-)-coniine.*

N-Acyl-2-alkyl-2,3-dihydro-4-pyridones **1** are readily available heterocycles[1] and useful synthetic intermediates for the preparation of indolizidine,[2] quinolizidine,[3] piperidine,[4] and *cis*-decahydroquinoline[5] alkaloids. We recently described a method for preparing these dihydropyridones enantiomerically pure via the addition of Grignard reagents to chiral 1-acylpyridinium salts.[6] The related 1-acyl-1,2-dihydropyridines **2** are also very useful building blocks for alkaloid synthesis,[7-9] and a reduction-elimination method ($NaBH_4/CeCl_3$; MsCl/DMAP) for converting enantiopure 2,3-dihydro-4-pyridones to 1, 2-dihydropyridines has been developed in our laboratories.[9]



1



2 X = H, Cl, OMe

The considerable synthetic potential of enantiopure heterocycles **2** has prompted us to investigate other methods for converting 2,3-dihydro-4-pyridones of the type **1** to 1-acyl-1,2-dihydropyridines. We now report this conversion via a simple, one-step procedure using a Vilsmeier reagent.

The action of formamide-derived Vilsmeier reagents on ketones and amides generally results in products containing a β-chlorovinyl aldehyde group.[10] As part of a study directed towards finding new ways to regioselectively substitute dihydropyridones, we decided to examine the Vilsmeier chloroformylation reaction of **1** (R^1 = Ph, R^2 = Bn). When we performed this reaction with excess Vilsmeier reagent, the vinyl chloride was obtained along with the expected 3-formyl-4-chloro derivative. This result indicated that the vinyl chloride was a likely intermediate in the formylation process and suggested a simple conversion of 1-acyl-2,3-dihydro-4-pyridones to 4-chloro-1,2-dihydropyidines (i.e. **4**) may be feasible. We were prompted to pursue conditions that would inhibit the second step of the reaction sequence. The use of only one equivalent of Vilsmeier reagent under mild conditions seemed to be a reasonable approach to obtaining the desired result. Reactions of several racemic 2,3-dihydro-4-pyridones **3** were investigated and the results are given in Table 1.

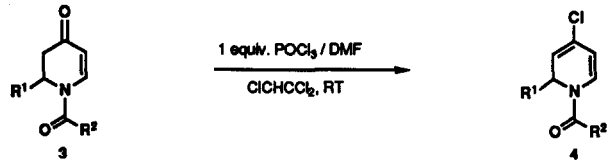
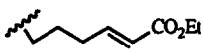
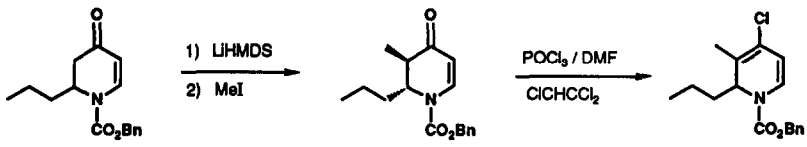


Table 1. Preparation of 4-Chloro-1,2-dihydropyridines 4.

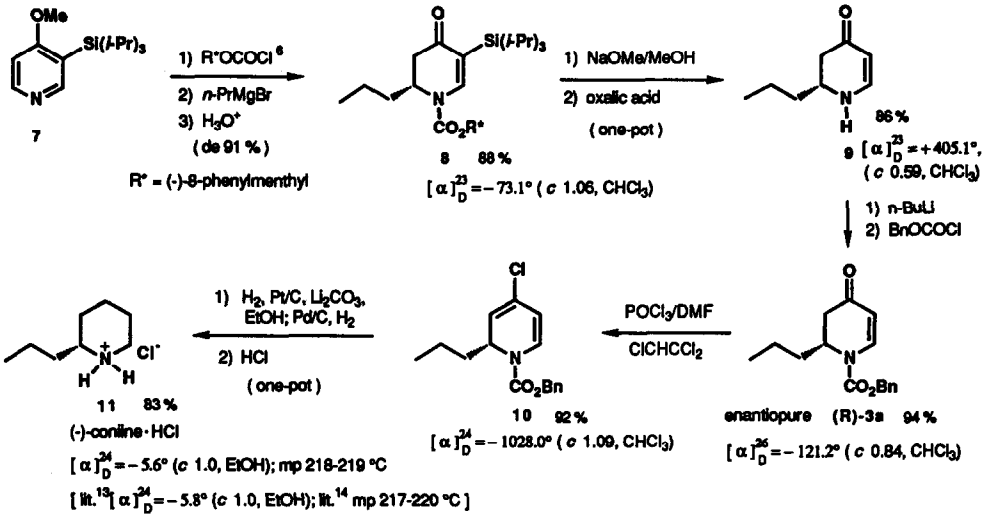
entry[a]	R^1	R^2	conditions[b]	yield,[c] %
a	n-Pr	OBn	$POCl_3$ (1 equiv.) DMF (1 equiv.) $ClCHCCl_2$, RT, 2-3d	96
b	c-Hex	$(CH_2)_3Br$	"	83
c	c-Hex		"	92
d	Ph	OBn	"	86
e		OBn	"	83

[a]The reactions were generally performed on a 1-2 mmol scale in trichloroethylene. [b]The workup consisted of concentration, addition of aqueous sodium bicarbonate, and extraction with methylene chloride. [c]Yield of products obtained from radial preparative-layer chromatography (silica gel, EtOAc/hexanes). Satisfactory IR, ^1H and ^{13}C NMR, and HRMS or microanalysis data were obtained for all compounds.

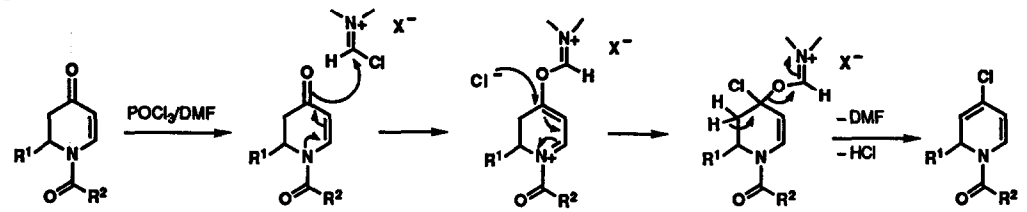
The reaction is very easy to perform and the yields of **4** are very good to excellent. Only small amounts (<5%) of formylated compounds were observed in the crude products by ^1H NMR. The reaction conditions are mild and compatible with various *N*-acyl groups. An α,β-unsaturated ester in the side chain (R^1) is also tolerated (entry e). To determine if this reaction would proceed in the presence of a C-3 alkyl group, the 2,3-dialkyl-2,3-dihydro-4-pyridone **5** was prepared and subjected to our chlorination reaction as shown below. Dihydropyridone **3a** was treated with LiHMDS/MeI to give the *trans*-2,3-dialkyl-2,3-dihydro-4-pyridone **5** in 87% yield.[2c] Reaction of **5** with $POCl_3$/DMF using our standard conditions (RT, 2 d) gave a 90% yield of 1,2-dihydropyridine **6**. Although 3-unsubstituted 1-acyl-4-chloro-1,2-dihydropyridines can be prepared by the addition of Grignard reagents to the 1-phenoxycarbonyl salt of 4-chloropyridine[11], the analogous reaction with a 3-alkyl-4-chloropyridine would lead to a mixture of regioisomers due to attack at C-2 and C-6 of the pyridinium salt.[7,12] Our three-step synthesis of **6** represents a regiospecific method for the preparation of 2,3-dialkyl-1,2-dihydropyridines of this type.

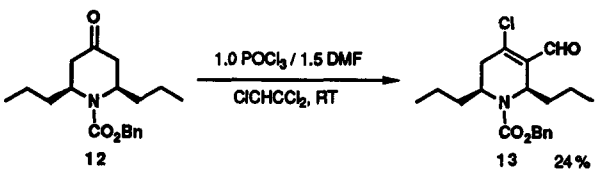


Combining our recently developed asymmetric synthesis of 2-alkyl-2,3-dihydro-4-pyridones[6] and the above methodology will allow the preparation of various enantiopure 1-acyl-4-chloro-1,2-dihydropyridines of ample synthetic potential.[7-9] In addition, this Vilsmeier reaction can be utilized in a facile, 2-step conversion of chiral dihydropyridones of the type **3a** to enantiopure 2-alkylpiperidines. This utility is demonstrated in the synthesis of (-)-coniine hydrochloride[13-14] (**11**) shown below.



Although the mechanism of reaction involving ketones and Vilsmeier reagents is not well understood, presumably α-iminoalkylation precedes vinyl chloride formation in most cases.[10] To explain the formation of 4-chloro-1,2-dihydropyridines **4** from 2,3-dihydropyridones **3** and $POCl_3$/DMF, the following mechanism is proposed.





It is noteworthy that treatment of dihydropyridone **3a** under the usual conditions *but in the absence of DMF* gave no reaction. Also, under the usual conditions, piperidone **12** and Vilsmeier reagent gave mainly recovered starting material and 24% yield of the ß-chlorovinyl aldehyde **13**.

Further studies on the synthetic utility of chiral dihydropyridones and 1, 2-dihydropyridines are in progress.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant GM 34442). R.A. also thanks the Burroughs Wellcome Fund for a graduate fellowship. The 300-MHz NMR spectra and mass spectra were obtained at NCSU instrumentation laboratories which were established by grants from the North Carolina Biotechnology Center.

References and Notes

1. Dihydropyridones **1** are conveniently prepared by the addition of Grignard reagents to 1-acyl-4-methoxypyridinium chloride, see: (a) Comins, D. L.; Brown, J. D. Tetrahedron Lett. **1986**, 27, 4549. (b) Comins, D. L.; LaMunyon, D. H. Tetrahedron Lett. **1989**, 30, 5053.
2. (a) Comins, D. L.; Hong, H. J. Am. Chem. Soc. **1991**, 113, 6672. (b) Comins, D. L.; Morgan, L. A. Tetrahedron Lett. **1991**, 32, 5919. (c) Comins, D. L.; Zeller, E. Tetrahedron Lett. **1991**, 32, 5889.
3. (a) Comins, D. L.; O'Connor, S. Tetrahedron Lett. **1987**, 28, 1843. (b) Brown, J. D.; Foley, M.A; Comins, D. L. J. Am. Chem. Soc. **1988**, 110, 7445. (c) See reference 1.
4. (a) Comins, D. L.; Foley, M. A. Tetrahedron Lett. **1988**, 29, 6711. (b) Chiral piperidines have been prepared from *N*-alkyl-2,3-dihydro-4-pyridones, see: Pfrengle, W.; Kunz, H. J. Org. Chem. **1989**, 54, 4261. Waldmann, H.; Braun, M.; Dräger, M. Angew. Chem. Int. Ed. Engl. **1990**, 29, 1468. Hattori , K; Yamamoto, H. J. Org. Chem. **1992**, 57, 3264 and references therein.
5. (a) Comins, D. L.; Abdullah, A. H.; Smith, R. K. Tetrahedron Lett. **1983**, 24, 2711. (b) Comins, D. L.; Abdullah, A. H. Tetrahedron Lett. **1986**, 26, 43. (c) Comins, D. L.; Dehghani, A. Tetrahedron Lett. **1991**, 32, 5697. (d) Comins, D. L.; Al-awar, R. S. J. Org. Chem. **1992**, 57, 4098.
6. Comins, D. L. ; Goehring, R. R. ; Joseph, S. P.; O'Connor, S. J. Org. Chem. **1990**, 55, 2574.
7. For reviews on dihydropyridines, see: Stout, D. M.; Meyers, A. I. Chem. Rev. **1982**, 82, 223. Sausins, A.; Duburs, G. Heterocycles **1988**, 27, 291. Also see: Comins, D. L. ; O'Connor, S. Adv. Heterocycl. Chem. **1988**, 44, 199.
8. (a) Yamaguchi, R. ; Hata, E.; Matsuki, T.; Kawanisi, M. J. Org. Chem. **1987**, 52, 2094. (b) Comins, D. L.; Myoung, Y. C. J. Org. Chem. **1990**, 55, 292. (c) Ogawa, M.; Natsume, M. Heterocycles **1985**, 23, 831. (d) Natsume, M.; Utsunomiya, I.; Yamaguchi, K.; Sakai, S. Tetrahedron **1985**, 41, 2115 and references therein. (e) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawansi, M. Bull.Chem. Soc. Jpn. **1987**, 60, 215. (f) Comins, D. L.; Weglarz, M. A. J. Org. Chem. **1991**, 56, 2506.
9. Comins, D. L.; Hong, H.; Salvador, J. M. J. Org. Chem. **1991**, 56, 7197.
10. For an excellent review on the reactions of carbonyl compounds with Vilsmeier reagents, see: Marson, C. M. Tetrahedron **1992**, 48, 3659.
11. Comins, D. L.; Mantlo, N. B. J. Org. Chem. **1985**, 50, 4410.
12. Comins, D. L.; Mantlo, N. B. Tetrahedron Lett. **1987**, 28, 759 and references therein.
13. Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H-P. J. Am Chem. Soc. **1983**, 105, 7754.
14. Ito, M.; Maeda, M.; Kibayashi, C. Tetrahedron Lett. **1992**, 33, 3765 and references therein.

(Received in USA 1 July 1992; accepted 11 August 1992)