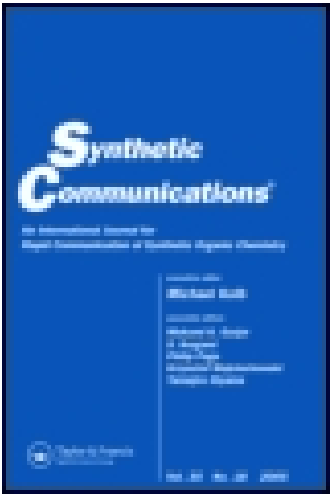


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 1,4-Dihydropyridines by Regioselective Additions of Benzylic Zinc Bromides to Pyridinium Salts and Their Aromatizations to 4-Benzylpyridines

A. Paul Krapcho [a], David J. Waterhouse [a], Abdelhakim Hammach [a], Roberto Di Domenico [b], Ernesto Menta [b], Ambrogio Oliva [b] & Silvano Spinelli [b]

[a] Department of Chemistry, University of Vermont, Burlington, VT, 05405, USA

[b] Boehringer Mannheim Italia, Research Center, Monza, 20052, Italy

Published online: 22 Aug 2006.

SYNTHETIC COMMUNICATIONS, 27(5), 781-794 (1997)

SYNTHESIS OF 1,4-DIHYDROPYRIDINES BY REGIOSELECTIVE ADDITIONS OF BENZYLIC ZINC BROMIDES TO PYRIDINIUM SALTS AND THEIR AROMATIZATIONS TO 4-BENZYLPYRIDINES

A. Paul Krapcho[a,*], David J. Waterhouse[a], Abdelhakim Hammach[a], Roberto Di Domenico[b], Ernesto Menta[b], Ambrogio Oliva[b] and Silvano Spinelli[b]

[a] Department of Chemistry, University of Vermont, Burlington, VT 05405, USA

[b] Boehringer Mannheim Italia, Research Center, Monza 20052, Italy

Abstract: Benzylic zinc reagents add with high regioselectivity to 1-(phenoxycarbonyl) salts of methyl nicotinate to yield methyl-1-(phenoxylcarbonyl)-4-benzyl-1,4-dihydronicotinates. The dihydronicotinates on heating with sulfur in decalin afford methyl 4-benzylnicotinates.

Introduction

The addition of an organometallic reagent to a pyridinium salt is a valuable preparative route to either 2- or 4-substituted dihydropyridines.[1] Aromatizations of these dihydropyridines lead to the respective 2- or 4-substituted pyridines.[1,2] The regioselectivity is highly dependent on the structure of the organometallic reagent and the nature and position of substituents on the pyridine ring.[1] Organocopper reagents, [1,3-6] mixed-organo-zinc-copper species[7] and benzylic tin reagents[8] regioselectively add

*To whom correspondence should be addressed

to the 4-position of 1-[(aryl- or alkoxy)carbonyl]pyridinium salts which hold no substituents at this position. Grignard reagents, on the other hand, add predominantly to the 2-position of pyridinium salts, with alkenyl and alkynyl Grignard reagents exhibiting remarkably high regioselectivities.[9b]

The regioselectivity of addition exhibited by the organometallic species towards pyridinium salts has been rationalized on the basis of HSAB principles.[7d,f,g,9a,10] It has been suggested that relatively hard nucleophiles preferentially attack the 2-position whereas softer nucleophiles prefer the 4-position. [7g,9a] In the mixed copper-zinc reagents,[11] it is noted that the softness of the nucleophilic site is dramatically increased, which then favors attack at the 4-position.[7f]

The carbon-zinc bond is highly covalent and quite comparable to a carbon-tin bond.[12] Inter- and intramolecular conjugate additions of organo zinc compounds[13] are known and alkyl zinc reagents, in a few cases, have been shown to add regioselectively to the 4-position of pyridinium salts.[9b,14] Since benzylic tin[8] and benzyl mixed copper-zinc species[7c,d] add predominately to the 4-position of these salts, of particular interest to our research was a study of benzyl zinc bromide additions to pyridinium salts.

Benzylic zinc bromides are readily prepared by treatment of benzylic bromides with Zn dust[7c,d,11,15] and are unreactive towards many functionalities. During their preparation only small amounts of dimer (cross-coupling product) are formed in contrast to the much higher amounts of dimer formed on treatment of benzylic bromides with Mg metal.[15]

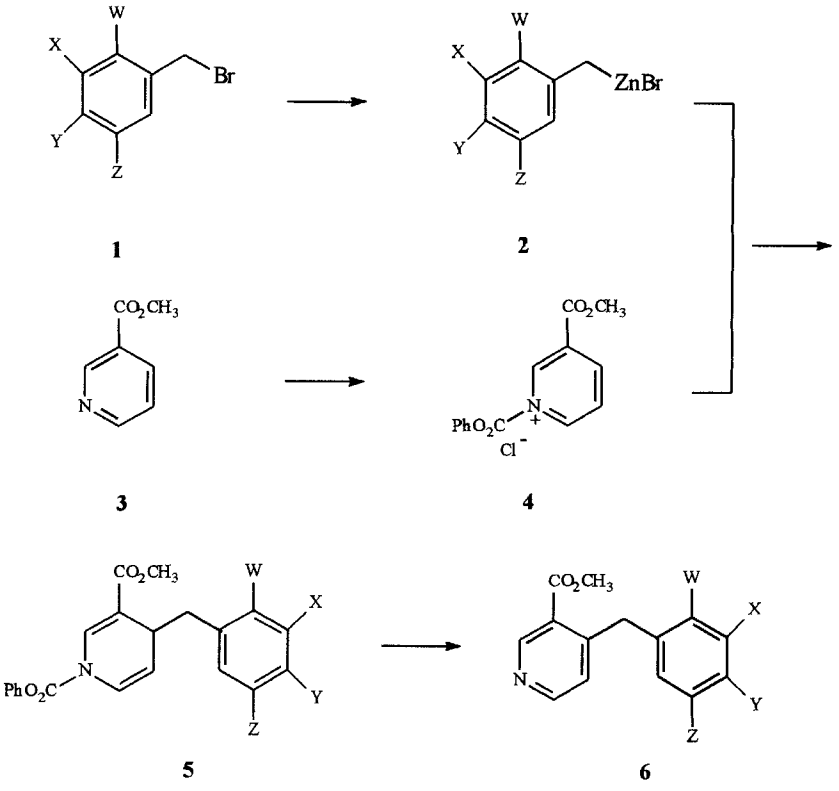
We have found that benzyl and substituted benzylic zinc bromides, in the absence of copper(I) salts, undergo highly regioselective additions to 1-(phenoxycarbonyl)pyridinium salts formed from methyl nicotinate to yield methyl 4-benzyl substituted-1,4-dihydro nicotinates in reasonable yields (Scheme 1).

The benzylic zinc bromides **2a-f** were prepared by treatment of the corresponding benzyl bromides **1a-f** with Zn dust[16] in tetrahydrofuran at room temperature.

The pyridinium chloride **4** was prepared by addition of phenyl chloroformate to a solution of methyl nicotinate (**3**) in tetrahydrofuran at 0°C. The appropriate benzylic zinc bromide solution (small amounts of unreacted Zn were usually present) was added via cannula under nitrogen pressure to **4** held at 0°C followed by aqueous workup to afford dihydropyridines **5a-f** (50-84% yields, Scheme 1, Table 1) as stable, crystalline solids.[17] Analysis of the crude reaction products obtained from these reactions by TLC or ^{1}H NMR spectroscopy indicated contamination by small amounts of dimer (δ, s, 2.9) formed during preparation of the organo zinc reagent and methyl nicotinate (**3**, δ, s, 3.9). Absorptions for protons indicative of the presence of other regioisomers were not detectable.

A more thorough study was performed using **2b**. Treatment of **4** with the mixed copper reagent prepared[7b] by addition of CuCN.2LiCl to **2b** followed by isolation led to the crude dihydropyridine **5b**, whose ^{1}H NMR spectrum was identical to that of the product isolated in the absence of the copper salt.

Scheme 1

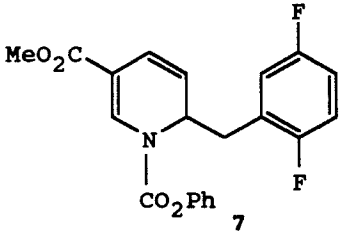


Structures 1,2,5,6	W	X	Y	Z
a	H	H	H	H
b	F	H	H	F
c	H	F	H	F
d	Cl	H	F	H
e	F	H	H	Cl
f	Cl	H	H	F

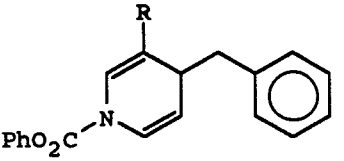
Table 1. Melting Points, Yields and ^{1}H NMR Data for Analogues **5**

5	mp, °C	% yield	^{1}H NMR δ, $CDCl_3$ (TMS)
a	90-91	60	8.02 (s, 1H), 7.2-7.5 (m, 10H), 6.85(d, 8Hz, 1H),5.1 (m, 1H), 3.80 (s, 3H), 3.62 (m, 1H), 3.05 (dd, 1H), 2.65 (dd, 1H)
b	77-78	50	8.04(s, 1H), 7.4(m, 2H), 7.3(m,1H), 7.1(m, 2H), 7.0(m, 1H), 6.9(m, 3H), 5.1(m, 1H), 3.80(s, 3H), 3.7(m, 1H), 2.9(dd, 1H), 2.8(dd, 1H)
c	78-79	60	8.05(s,1H), 7.4(m, 2H), 7.3(m, 1H), 7.2(m, 2H), 6.9(m, 1H), 6.7(m, 3H), 5.1(m, 1H), 3.81(s, 3H), 3.6(m, 1H), 3.0(dd, 1H), 2.6(dd, 1H)
d	105-106	72	8.06(s, 1H), 7.4(m, 2H), 7.3(m, 1H), 7.1(m, 4H), 6.9(m, 2H), 5.1(m, 1H), 3.76(m+s, 1H + 3H), 3.1(dd, 1H), 2.9(dd, 1H)
e	78-79	50	8.03(s, 1H), 7.4(m, 2H), 7.3(m, 1H), 7.1(m, 1H), 6.9(m, 2H), 5.1(br, m, 1H), 3.80(s, 3H), 3.7(m, 1H), 2.9(dd, 1H), 2.85(dd, 1H)
f	70-72	84	8.1(brs, 1H), 7.4(m, 2H), 7.3(m, 2H), 7.2(m, 2H), 6.9(m, 3H), 5.1(m, 1H), 3.8(m + s, 1H + 3H), 3.27(dd, 1H), 2.85(dd, 1H)

On the other hand, treatment of **1b** with Mg metal in ether and then CuI (0.03 equivalents), followed by addition of this benzylic organic reagent to pyridinium salt **4** in tetrahydrofuran (-50°C) led predominantly to **5b.** However, the 6-(2,5-difluorobenzyl) regioisomer **7** (15%) could also be isolated. Similar yields of **7** (10-12%) were found by use of Li_2CuCl_4 (0.1M in THF, 0.03 equivalents) or CuI (0.3 equivalents) as catalyst and performing the addition at -20°C.



7



8 a, R = H
b, R = CH_3

The dihydropyridines **5a-f** on being heated with sulfur in refluxing decalin led to the corresponding pyridines **6a-f** in good yields (Scheme 1, Table 2).

Treatment of the 1-(phenoxycarbonyl)pyridinium salts formed from pyridine and 3-methyl pyridine with benzyl zinc bromide (**1b**) led to the corresponding dihydropyridines **8a** and **8b** in good yield. Analysis of the ^1H NMR spectrum of **8a** or **8b** indicated only possible trace contamination by the 2-regioisomers. The crude products **8a** and **8b** were aromatized by heating with sulfur in decalin to yield only 4-benzylpyridine (60%, >98% purity)[18] and 3-methyl-4-benzylpyridine (60%).[19] Based on these results, the regioselectivity exhibited by the benzylic zinc bromides is clearly not attributable to the presence of the carbomethoxy group on the pyridine ring.

Table 2. Melting Points, Yields and ^1H NMR data for Analogues **6**

6	mp, °C	% yield	^1H NMR δ, $CDCl_3$ (TMS)
a	oil	60	9.08(s, 1H), 8.56(d, J=5.2 Hz, 1H), 7.2(m, 5H), -7.1(d, J=5Hz, 1H), 4.40(s,2H), 3.90(s, 3H)
b	83-84	76	9.13(s, 1H), 8.61(d, J=5Hz, 1H), 7.1(d, J=5Hz, 1H), 7.0(m, 1H), 6.9(m, 1H), 6.8(m, 1H), 4.41(s, 2H), 3.92 (s, 3H)
c	52-53	63	9.15(s, 1H), 8.64(d, J=5Hz, 1H), 7.1(d, J=5Hz, 1H), 6.7(m, 3H), 4.38(s, 2H), 3.91(s, 3H)
d	71-72	75	9.13(s, 1H), 8.57(d, J=5Hz, 1H), 7.2(m, 1H), 7.0(m, 1H), 6.9(m, 2H), 4.48(s, 2H), 3.92(s, 3H)
e	82-83	50	9.13(s, 1H), 8.61(d, J=5Hz, 1H), 7.20(m, 1H), 7.0(m, 3H), 4.40(s, 2H), 3.93(s, 3H)
f	60-62	70	9.18(s, 1H), 8.6(d, J=5Hz, 1H), 7.4(m, 1H), 6.98(d, J=5Hz, 1H), 6.95(m, 1H), 6.75(m, 1H), 4.5(s, 2H), 3.95(s, 3H)

Conclusions

The readily preparable benzylic zinc bromides show high regioselectivity in additions to pyridinium salts to yield 4-benzyl substituted-1,4-dihydropyridines. Aromatizations of these analogues readily affords 4-benzyl substituted pyridines.

Experimental

Benzyl bromides were purchased from Aldrich (**1a-c**), Lancaster (**1d**) and **1e** was prepared by a literature procedure[20] which was adapted for the synthesis of **1f**. Zinc dust (Aldrich, 32,493-0, 99.998% purity) was used as received. Tetrahydrofuran was freshly distilled from sodium metal. All reactions were performed under a nitrogen atmosphere using standard septa techniques. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton NMR were recorded on a Bruker WM-250 or ARX-500 pulsed spectrometer. Satisfactory analytical data were obtained for all new compounds and are listed in Table 3.

Typical Dihydropyridine Preparative Procedure: Methyl-1-(phenoxycarbonyl)-4-(2,5-difluorobenzyl)-1,4-dihydronicotinate (5b)

A solution of **1b** (1.02 g, 4.9 mmol) in THF (6 mL, freshly distilled from sodium metal) was added dropwise over a 5-minute period to a suspension of zinc dust (0.32 g, 4.94 mmol) in THF (4 mL). The mixture was kept in a water bath at room temperature and allowed to stir for 4 hours. To a solution of **3** (0.73 g, 5.35 mmol) in THF (10 mL) held in an ice bath, phenyl chloroformate (0.64 mL, 5.1 mmol) was added dropwise over a 5-minute period. The mixture was stirred for 1 hour in an ice bath. The organo zinc bromide **2b** was added to the cold phenoxycarbonyl pyridinium chloride solution **4** over a 10-minute period via a cannula and the mixture was stirred for 1 hour. The mixture was warmed to room temperature and quenched into aqueous ammonium chloride

Table 3. Analytical Data

	Molecular formula	CALCD %C	CALCD %H	CALCD %N	FOUND %C	FOUND %H	FOUND %N
5a	$C_{21}H_{19}NO_4$	72.19	5.48	4.00	72.01	5.45	3.95
5b	$C_{21}H_{17}F_2NO_4$	65.45	4.45	3.64	65.20	4.34	3.72
5c	$C_{21}H_{17}F_2NO_4$	65.45	4.45	3.64	65.42	4.31	3.54
5d	$C_{21}H_{17}C\ell FNO_4$	62.77	4.26	3.49	62.50	4.30	3.38
5e	$C_{21}H_{17}C\ell FNO_4$	62.77	4.26	3.49	62.57	4.16	3.44
5f	$C_{21}H_{17}C\ell FNO_4$	62.77	4.26	3.49	62.67	4.18	3.45
6b	$C_{14}H_{11}F_2NO_2$	63.88	4.21	5.32	63.78	4.25	5.35
6c	$C_{14}H_{11}F_2NO_2$	63.88	4.21	5.32	63.86	4.19	5.23
6d	$C_{14}H_{11}C\ell FNO_2$	60.11	3.96	5.00	60.30	3.76	5.01
6e	$C_{14}H_{11}C\ell FNO_2$	60.11	3.96	5.00	60.20	3.80	4.98
6f	$C_{14}H_{11}C\ell FNO_2$	60.11	3.96	5.00	60.15	3.76	5.09
7	$C_{21}H_{17}F_2NO_4$	65.45	4.45	3.64	65.25	4.35	3.62

(20%, 12 mL). The product was extracted with ethyl acetate (2 x 30 mL) and the extract washed with aqueous sodium bicarbonate (10%, 10 mL), water (20 mL), aqueous ammonium chloride (20%, 10 mL) and then water (20 mL). The extract was dried over sodium sulfate, decanted from the drying agent and

concentrated by rotary evaporation to yield a viscous oil (1.77 g). Analysis of this crude product by ^{1}H NMR indicated the presence of some dimer, unreacted **3** and no proton absorptions for other regioisomers. This crude material crystallized readily from pentane or mixtures of hexane and ethyl acetate.

Analogues **5a** and **5c-f** were prepared in a similar manner and the melting points, yields and ^{1}H NMR data for dihydropyridines **5** are tabulated in Table 1. Analytical data for these compounds are tabulated in Table 3.

Methyl-1-(phenoxycarbonyl)-6-(2,5-difluorobenzyl)-1,4-dihydronicotinate (7)

Magnesium turnings (0.53 g, 22 mmol) were washed with dry THF and covered with dry ether (20 mL). A crystal of iodine and 1 mL of a solution of **1b** (2.3 g, 11 mmol) in ether (30 mL) was added to the suspension, and when the suspension became colorless, the remaining solution was added at such a rate to maintain a slight reflux (35 minutes). Methyl nicotinate (**3**, 1.37g, 10 mmol) in THF (30 mL) was cooled to -20°C and treated with phenyl chloroformate (1.32 mL, 10.5 mmol) over a period of 15 minutes. The resultant mixture was stirred for 45 minutes and copper(I) iodide (50 mg, 0.26 mmol) was added and the temperature lowered to -50°C. The Grignard solution was added to the pyridinium salt solution via a Teflon cannula by means of a nitrogen pressure and after stirring at -50°C for 15 minutes, the mixture was allowed to warm to room temperature. The mixture was concentrated under vacuum and dichloromethane (50 mL) and ammonium chloride (20%, 50 mL)

were added. The resultant emulsion was filtered through celite and the organic filtrate washed with aqueous sodium hydroxide (1N) , twice with aqueous sodium chloride (20 mL) and dried over sodium sulfate. The clear solution was concentrated under vacuum and the oily residue purified by flash chromatography (petroleum ether: diisopropyl ether from 95:5 to 90:10) to yield an oily residue consisting mainly of **5b** and an oily mixture of **5b** and **7**. This mixture was crystallized from petroleum ether: diisopropyl ether 20:1 and then diisopropyl ether to yield pure **7** (0.58 g, 15%); mp 108-110°C.

^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.4 (m, 2H), 7,2 (m, 1H), 6.9 (overlapping m, 5H), 6.5 (m, 1H), 5.6 (m, 1H), 5.3 (m, 1H), 3.8 (s, 3H), 3.0 (m, 1H), 2.8 (m, 1H).

Typical Aromatization Procedure

Methyl-4-(2,5-difluorobenzyl)nicotinate (6b)

Dihydropyridine **5b** (0.50 g, 1.30 mmol) and sulfur (0.042 g, 1.31 mmol) in decalin (3 mL) were refluxed for 5 hours. The mixture was allowed to cool to room temperature and the pyridine was extracted into hydrochloric acid (3%, 4 x 4 mL). The aqueous extract was basified by addition of aqueous sodium hydroxide (10%) and the product was extracted with dichloromethane (4 x 8 mL). The extract was dried over sodium sulfate and concentrated by rotary evaporation to yield **6b** (0.26 g) as a brownish oil which solidified. Analysis of this material by ^{1}H NMR indicated substantially pure product. The crude product was heated in pentane and treated with silica gel and decolorizing charcoal to yield pure crystalline **6b**.

Pyridines **6a**[7d] and **6c-f** were prepared by adaptation of the typical procedure and the melting points, yields and ^{1}H NMR data for analogues **6** are listed in Table 2. Microanalytical data for **6b-f** are tabulated in Table 3.

References and Notes

1. (a) Comins, D.L. and O'Connor, S. Adv. Heterocyclic Chem. **1988**, 44, 199. This review presents an excellent literature survey through mid 1987.
   (b) Stout, D.M. and Meyers, A.I. Chem. Rev. **1982**, 82, 223.

2. Sausins, A. and Duburs, G. Heterocycles **1988**, 27, 291.

3. Piers, E. and Soucy, M. Can. J. Chem. **1974**, 52, 3563.

4. (a) Comins, D.L. and Abdullah, A. H. J. Org. Chem. **1982**, 47, 4315.
   (b) Comins, D.L. and Mantlo, N.B. J. Heterocyclic Chem. **1983**, 20, 1239.
   (c) Comins, D.L.; Smith, R.K. and Stroud, E.D. Heterocycles **1984**, 22, 339.
   (d) Comins, D.L.; Stroud, E.D. and Herrick, J.J. Heterocycles **1984**, 22, 151.
   (e) Comins, D.L.; Hong, H. and Salvador, J.M. J. Org. Chem. **1991**, 5, 7197.
   (f) Comins, D.L. and Stroud, E.D. J. Heterocyclic Chem. **1985**, 22, 1419.

5. (a) Akiba, K.; Iseki, Y. and Wada, M. Tetrahedron Lett. **1982**, 23, 429.
   (b) Akiba, K.; Iseki, Y. and Wada, M. Bull. Chem. Soc. Jpn. **1984**, 57, 1994.
   (c) Akiba, K. Bull. Soc. Chim. Belg. **1992**, 101, 339.

6. (a) Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M. and Alexakis, A. J. Org. Chem. **1994**, 59, 1877.
   (b) Mangeney, P.; Gosmini, R.; Raussou, S. and Commercon, M. Tetrahedron Lett. **1993**, 34, 6399.

7. (a) Shiao, M.-J. and Tarng, K.-Y. Heterocycles **1990**, 31, 637.
   (b) Shiao, M.-J. and Chia, W.-L. Synth. Commun. **1991**, 21, 401.
   (c) Chia, W.-L. and Shiao, M.-J. Tetrahedron Lett. **1991**, 32, 2033.
   (d) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J. and Chau, T.-Y. Synthesis **1991**, 849.
   (e) Shiao, M.-J.; Liu, K.-L. and Lin, L.-G. Synlett. **1992**, 655.
   (f) Shiao, M.-J.; Chia, W.-L.; Shing, T.-L. and Chow, T.J. J. Chem. Research (S) **1992**, 247; J. Chem. Research (M) **1992**, 2101.

(g) Shiao, M.-J.; Chia, W.-L.; Peng, C.-J. and Shen, C.-C. J. Org. Chem. **1993**, 58, 3162.

8. Yamaguchi, R.; Moriyasu, M. and Kawanisi, M. Tetrahedron Lett. **1986**, 27, 211.

9. (a) Yamaguchi, R.; Nakazono, Y. Matsuki, T.; Hata, E.-I. and Kawanisi, M. Bull. Chem. Soc. Jpn. **1987**, 60, 215.
(b) Yamaguchi, R.; Nakazono, Y. and Kawanisi, M. Tetrahedron Lett. **1983**, 24, 1801.

10. Doddi, G.; Ercolani, G. and Mencarelli, D. J. Org. Chem. **1992**, 57, 4431.

11. Knochel, P. and Singer, R.D. Chem. Rev. **1993**, 93, 2117.

12. Negishi, E. "Organometallics in Organic Syntheses", Wiley, New York, **1980**.

13. Bronk, B.S.; Lippard, S.J. and R.L. Danheiser, R.L. Organometallics **1993**, 12, 334 and references cited therein.

14. Comins, D.L. and O'Connor, S. Tetrahedron Lett. **1987**, 28, 1843.

15. (a) Jubert, C. and Knochel, P. J. Org. Chem. **1992**, 57, 5425.
(b) Berk, S.C.; Yeh, M.C.P.; Jeong, N. and Knochel, P. Organometallics **1990**, 9, 3053.
(c) Berk, S.C.; Knochel, P. and Yeh, M.C.P. J. Org. Chem. **1988**, 53, 5789.
(d) Chen, H.G.; Hoechstetter, C. and Knochel, P. Tetrahedron Lett. **1989**, 30, 4795.

16. High purity zinc dust (99.988%, Aldrich, -100 mesh) was utilized to minimize potential effects of copper catalysis from zinc activated on treatment with copper sulfate and hydrochloric acid.

17. Prior studies (references 4d, 7b and 7d) merely report the aromatizations of the crude dihydropyridines.

18. ^{1}H NMR analysis of authentic 2-benzyl- and 4-benzylpyridine indicated that as little as 2-3% of 2-benzylpyridine(δ, CH_2, s, 4.2) could be detected in 4-benzyl pyridine (δ, CH_2, s, 3.9).

19. ^{1}H NMR comparison of the data with that reported by Shiao in reference 7d.

20. Shepard, K.L.; Graham, S.L.; Hudcosky, R.J.; Michelson, S.R.; Scholtz, T.H.; Schwam, H.; Smith, A.M.; Sondey, J.M.; Strohmaier, K.M.; Smith, R.L. and Sugrue, M.F. J. Med. Chem. **1991**, 34, 3098.

(Received in the USA 16 September 1996)