Tetrahedron Letters,Vol.29,No.51,pp 6711-6714,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

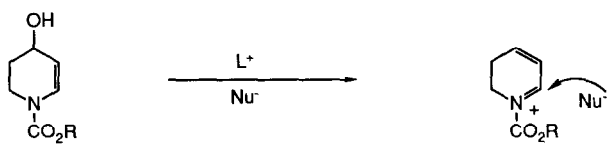
THE ADDITION OF ALKYLZINC IODIDES TO 1-(PHENOXYCARBONYL)-2,3-DIHYDRO-PYRIDINIUM SALTS. A SYNTHESIS OF 2-ALKYL-Δ^3-PIPERIDINES.

Daniel L. Comins* and Michael A. Foley

Department of Chemistry and Biochemistry
Utah State University, Logan, Utah 84322-0300

Summary: *Several 2-alkyl-1-(phenoxycarbonyl)-Δ^3-piperidines were prepared by the addition of alkylzinc iodides to 1-(phenoxycarbonyl)-2,3-dihydropyridinium salts.*

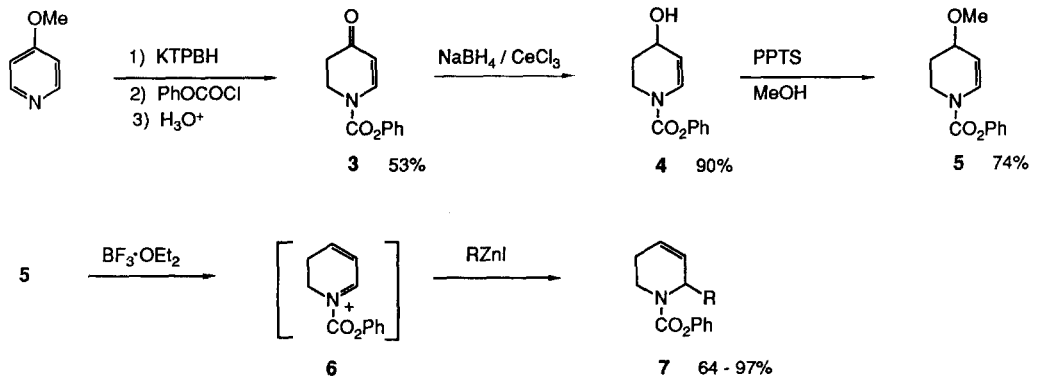
As part of a program aimed at studying the addition of nucleophiles to 1-acylpyridinium salts[1], we recently examined and reported the reaction of various organozinc iodides with 1-(phenoxycarbonyl)pyridinium chlorides. We found that in the absence of a substituent at the 4-position of the 1-acylpyridinium salt, the reaction was not very regioselective giving a mixture of 1,2- and 1,4-dihydropyridines.[1c] It appeared from examination of the literature that a higher degree of α-addition might be achieved if a 1-acyl-2,3-dihydropyridinium salt were the reactive intermediate. Kozikowski[2] and we[3] have shown that γ-hydroxy enecarbamates are valuable N-acyliminium ion precursors, and that 1-acyl-4-hydroxy-1,2,3,4-tetrahydropyridines **1** can be converted to 1-acyl-2,3-dihydropyridinium salts **2** in situ by treatment with a Lewis acid. Attack by soft nucleophiles, i.e. allyltrimethylsilane and silyl enol ethers, gives mainly



1 R = alkyl, aryl **2**

addition at the α-site of the conjugated iminium ion.[2] Since the presence of the γ-hydroxy group prohibits the use of organometallics as nucleophiles, we prepared the analogous γ-methoxy compound with the intent to use the methoxy function as a trigger for the in situ formation of the conjugated iminium ion in the presence of an alkylzinc reagent. The desired intermediate **5** was prepared by a modification of Kozikowski's procedure.[2] The addition of phenyl chloroformate to 4-methoxypyridine and potassium triisopropoxyborohydride (KTPBH) in isopropanol at -23 °C gave a 53% yield of dihydropyridone **3** on acidic workup. The analogous reaction using sodium borohydride as the reducing agent gave **3** in 34% yield. The dihydropyridone **3** was cleanly converted to the 4-hydroxy derivative **4** with $NaBH_4/CeCl_3$.[4] Treatment of **4** with pyridinium p-

toluenesulfonate (PPTS) in methanol gave the 4-methoxy-1,2,3,4-tetrahydropyridine 5 in good yield.



The reactive N-acyliminium ion intermediate **6** was generated in situ by adding $BF_3{\cdot}OEt_2$ to **5** and an organozinc reagent[5] in benzene at room temperature. The organozinc iodides added to the α-position of **6** to give the 2-alkyl-Δ^3-piperidines **7** in good to excellent yield as shown in the Table. A short reaction time (10 min) was essential as decomposition of the products occurred on prolonged exposure to the Lewis acid.

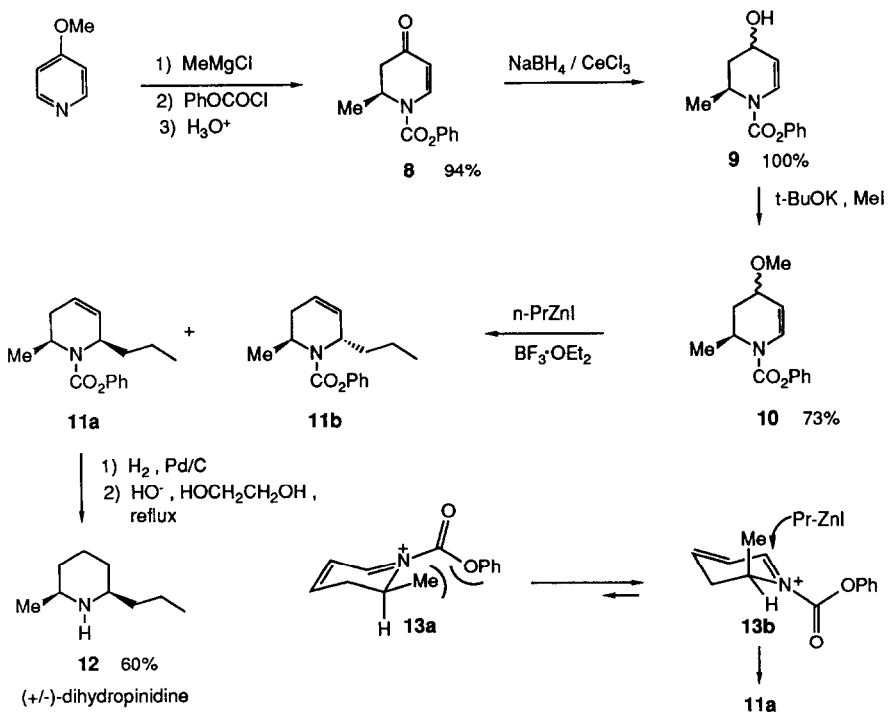
A modification of this method can be used to prepare cis-2,6-dialkyl-Δ^3-piperidines. The addition of phenyl chloroformate to a mixture of 4-methoxypyridine and methylmagnesium chloride in tetrahydrofuran (THF) followed by workup with 10% HCl gave a 94% yield of dihydropyridone **8**.[6] Reduction using $NaBH_4/CeCl_3$ provided the alcohol **9** in quantitative yield. Without purification, **9** was converted to methyl ether **10** with t-BuOK/MeI in THF (-78°C to RT, 1h). Treatment of **10** with n-propylzinc iodide (4 equiv) and $BF_3{\cdot}OEt_2$ (4 equiv, benzene, RT, 10 min) gave a 90% yield of cis- and trans-2,6-dialkyl-Δ^3-piperidines **11a** and **11b** in a ratio of 4:1. The major diastereomer **11a** was isolated (SiO_2, 5% EtOAc/hexanes) and its relative stereochemistry assigned as shown based on NMR analysis[7]. The cis-stereochemistry of **11a** was confirmed by conversion (reduction followed by hydrolysis) to (±)-dihydropinidine (**12**) [hydrochloride m.p. 212-213°C (lit.[8] m.p. 210-213°C)].

The stereoselectivity of the alkylzinc reaction leading to **11a** likely arises from a stereoelectronic effect. Due to a strong $A^{(1,3)}$ strain between the methyl group at C-2 and the N-acyl group of iminium ion **13a**, the methyl group of **13** will occupy the axial position via conformation **13b**.[9] Stereoelectronically preferred[10] axial attack on **13b** by the alkylzinc iodide gives the cis-2,6-dialkyl-Δ^3-piperdine **11a** as the major product.

Table. Synthesis of 2-Alkyl-Δ^3-piperidines **7** from **5**.

Entry	RZnI[a]	Product **7**[b] R	Yield[c]
a	MeZnI	Me	93
b	n-BuZnI	n-Bu	71
c	$Cl(CH_2)_4ZnI$	$(CH_2)_4Cl$	77
d	$EtO_2C(CH_2)_2ZnI$	$(CH_2)_2CO_2Et$	97
e	$EtO_2C(CH_2)_3ZnI$	$(CH_2)_3CO_2Et$	82
f	$EEO(CH_2)_3ZnI$[d]	$(CH_2)_3OH$	64

[a]Reactions were performed by adding the alkylzinc iodide (benzene-DMA)[5] to **5** in benzene at RT followed by 1.5 equiv of $BF_3{\cdot}OEt_2$. After stirring at RT for 10 min aqueous HCl was added. Extraction with ether provided the crude products. [b]All products gave the expected IR and NMR spectra and elemental analysis. [c]Yields are of purified products obtained from radial-PLC (SiO_2, ethyl acetate/hexanes). [d]EE = 1-Ethoxyethyl.



Acknowledgement We wish to express appreciation to the National Institutes of Health for support of this research (Grant GM 30255). High-field NMR spectra were obtained using a Varian XL-300 spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-8417529).

References and Notes

1. (a) D. L. Comins, M. A. Weglarz, and S. O'Connor, Tetrahedron Lett., **29**, 1751 (1988). (b) D. L. Comins and J. J. Herrick, Heterocycles, **26**, 2159 (1987). (c) D. L. Comins and S. O'Connor, Tetrahedron Lett., **28**, 1843 (1987) and references therein.
2. A. P. Kozikowski and P-u. Park. J. Org. Chem., **49**, 1674 (1984).
3. D. L. Comins and A. H. Abdullah, Tetrahedron Lett., **26**, 43 (1985); D. L. Comins and E. D. Stroud, Tetrahedron Lett., **27**, 1869 (1986).
4. J.-L. Luche, J. Am. Chem. Soc., **100**, 2226 (1978).
5. Y. Tamaru, H. Ochiai, F. Sanda, and Z. Yoshida, Tetrahedron Lett., **26**, 5529 (1985); Y. Tamaru, H. Ochiai, T. Nakamura, K. Tsubaki, and Z. Yoshida, ibid., **26**, 5559 (1985); Y. Tamaru, H. Ochiai, T. Nakamura, and Z. Yoshida, ibid., **27**, 955 (1986).
6. D. L. Comins and J. D. Brown, Tetrahedron Lett., **27**, 4549 (1986).
7. Spectral data for **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.1 (m, 5H), 5.8 (s, 2H), 4.8 (t, 1H, J = 6 Hz), 4.4 (m, 1H), 2.5 (m, 1H), 1.95 (dd, 1H, J = 6 Hz) and J = 18 Hz), 1.9-1.35 (m, 4H), 1.27 (d, 3H, J = 7), 0.96 (t, 3H, J = 7); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 151.8, 129.6, 129.5, 126.5, 125.3, 122.1, 121.8, 52.4, 44.5, 39.2, 30.4, 21.3, 20.4, 14.4; IR (neat) 3040, 2872, 1718, 1595, 1495, 1456, 1411, 754 cm^{-1}.
8. R. K. Hill and T. Yuri, Tetrahedron, **33**, 1569 (1977).
9. The $A^{(1,3)}$ strain in N-acylpiperidines has been demonstrated to make the 2-axial-substituted conformers more stable than the corresponding 2-equatorial isomers. P. Beak and W. J. Zajdel, J. Am. Chem. Soc., **106**, 1010 (1984) and references therein.
10. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry", Pergamon: New York, 1983; Chap. 6.

(Received in USA 7 September 1988)