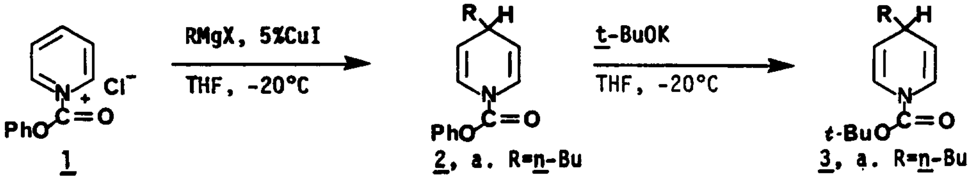
Tetrahedron Letters,Vol.24,No.28,pp 2807-2810,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

α-METALATION OF 1-(TERT-BUTOXYCARBONYL)-1,4-DIHYDROPYRIDINES

Daniel L. Comins
Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322

Summary: The α-metalation-alkylation of 4-substituted 1-(tert-butoxycarbonyl)-1,4-dihydropyridines is described. Subsequent aromatization provides a new route to 2,4-disubstituted pryidines.

We recently described a convenient method for the synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines via the regioselective addition of Gringard reagents to 1-acylpyridinium salts in the presence of a catalytic amount of cuprous iodide.[1]. The potential of these compounds as synthetic intermediates[2] has prompted us to develop methodology for elaborating the 4-substituted 1,4-dihydropyridine nucleus. We report here an α-metalation[3,4] of 4-substituted 1-(tert-butoxycarbonyl)-1,4-dihydropyridines 3 prepared from 1-phenoxycarbonylpyridinium chloride[5] (1) as shown below.



Addition of n-butylmagnesium chloride to the 1-acylpyridinium salt 1 and 5% CuI in THF (-20°C) gave the 1,4-dihydropyridine 2a (95%) after bulb-to-bulb distillation (bp 135-155 /0.6 mm). The 1-phenoxycarbonyl substituent of 2a would not be stable to the alkylithium reagent needed for α-metalation, thus 2a was converted to the N-BOC derivative 3a in high yield (85%) with potassium tert-butoxide in THF.[6]

Treatment of 3a with 1.2 equiv of sec-BuLi in THF at -42°C for 3h gave the α-lithiated dihydropyridine 4 which was reacted with various electrophiles (E) to give 2,4-disubstituted dihydropyridines 5 in high yield as shown in the table.

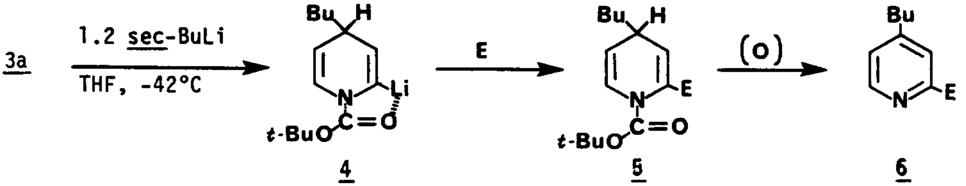
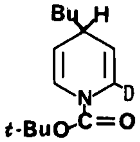
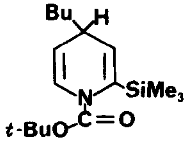
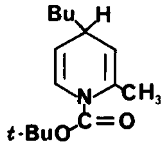
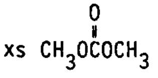
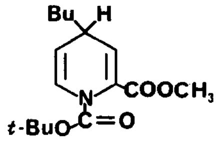
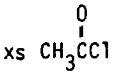
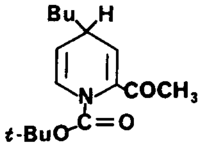
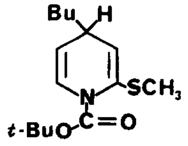


Table. Reaction of α-Lithiated 1,4-dihydropyridine 4 with Electrophiles

Entry	Electrophile	Reaction Conditions[a]	Product(5)[b]	Yield[c]
a	D_2O	-42° → RT		85%
b	TMSCl	-42°C, 30 min → RT		85%
c	CH_3I	-42°C, 1h		72%
d	 xs $CH_3O\overset{O}{\overset{\Vert}{C}}OCH_3$	0°C, 30 min		89%
e	 xs $CH_3\overset{O}{\overset{\Vert}{C}}Cl$	-78°C, 30 min → RT		70%
f	CH_3SSCH_3	-42°C, 1h		83%

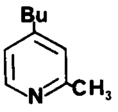
---

[a] Reactions were performed on a 3 mmol scale in 6 ml of THF. The workup consisted of quenching with brine followed by extraction with ether.

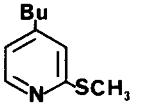
[b] All products gave the expected IR and ^1H NMR spectra. Due to their instability at room temperature, the dihydropyridines 5 were not submitted for C, H and N analysis.

[c] Yields are for isolated, pure, material obtained from radial preparative layer chromatography (silica gel, ethyl acetate-hexanes).

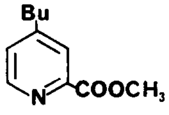
Oxidation of dihydropyridines 5 give 2,4-disubstituted prydines (6). Treatment of crude 5c and 5f with *o*-chloranil[7] in acetic acid (RT) gave 4-butyl-2-methylpyridine (6c) (65% from 3a) and 4-butyl-2-(methylthio)pyridine (6f) (79% from 3a) respectively. Dihydropyridine 5d was aromatized with sulfur[5] in refluxing decalin (3h) to give methyl 4-butylpicolinate (6d) (57%).



6c

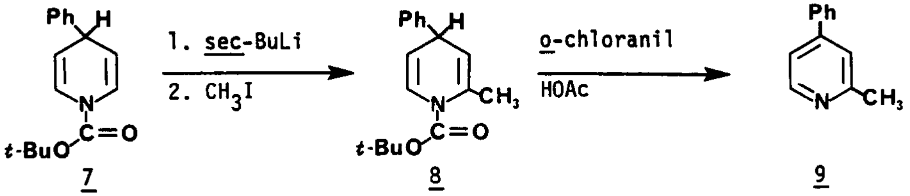


6f



6d

The α-metalation can also be performed on 4-aryl-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines. Initially we anticipated possible competing metalation at the benzylic position, for Schlosser[8] reported the abstraction of a methylene proton from N-methyl-1,4-dihydropyridine with [(trimethylsilyl)methyl]potassium to give an 8 π system (antiaromatic). However, competing metalation was not a problem as 4-phenyl-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine (7) gave the α-methylated derivative 8 in 80% yield. Aromatization of 8 with *o*-chloranil in acetic acid gave 4-phenyl-2-picoline (9)(82%).



Further investigations of the synthetic utility of these 1,4-dihydropyridines (2-5,7,8) are currently in progress.

Acknowledgements. We wish to express appreciation to the National Institute of General Medical Sciences of the NIH for support of this project from Grant GM 30255. Financial assistance from a Utah State University Faculty Research Grant (Mineral Lease, Project No. FAC-SC-13) is also acknowledged.

References and Notes:

1. D. L. Comins and A. H. Abdullah, J. Org. Chem., 47, 4315 (1982).

2. For reviews see D. M. Stout and A. I. Meyers, Chem. Rev., 82, 223 (1982); R. E. Lyle in "Pyridine and its Derivatives", Vol. 14, Part 1, R. A. Abramovitch, Ed., Wiley, New York, 1974, P. 137; U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).

3. 3-Cyano-1-methyl-1,4-dihydropyridine is metalated at the 2-position with lithium diisopropylamide. R. Schmidt and G. Berger, Chem. Ber., 109, 2936 (1976).

4. When 1-phenyl-1,4-dihydropyridine is treated with excess *n*-butyllithium, dilithiation occurs at the α-positions. A. I. Meyers, D. M. Stout, and T. Takaya, J. Chem. Soc., Chem. Commun., 1260 (1972); D.M. Stout, T. Takaya, and A. I. Meyers, J. Org. Chem., 40, 563 (1975).

5. R. E. Lyle and D. L. Comins, J. Org. Chem., 41, 3250 (1976).

6. 1-(Phenoxycarbonyl)-1,2-dihydropyridine has been converted to a 4:1 mixture of 1-(*tert*-butoxycarbonyl)-1,2- and -1,4-dihydropyridines with potassium *tert*-butoxide in THF. R. J. Sundberg and J. D. Bloom, J. Org. Chem., 46, 4836 (1981).

7. Chloranil has been used to aromatize dihydropyridines. See R. C. Fuson and J. J. Miller, J. Amer. Chem. Soc., 79, 3477 (1957); Y. Omote, T. Komatsu, R. Kobayashi, and N. Sugiyama, Tetrahedron Lett., 93 (1972); R. Dommisse, H. Desseyn, and F. Alderweireldt, Spectrochim. Acta, 29, 107 (1973).

8. M. Schlosser and P. Schneider, Angew. Chem. Int. Ed. Engl, 18, 489 (1979).

(Received in USA 7 April 1983)