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α-METALATION OF 1-(TERT-BUTOXYCARBONYL)-1,2-DIHYDROPYRIDINES

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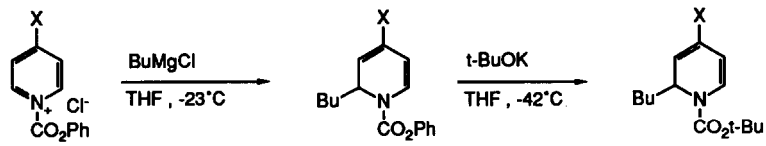
Summary: *The α-metalation-alkylation of 1-(tert-butoxycarbonyl)-1,2-dihydropyridines is described and utilized in the synthesis of (±)-epi-myrtine.*

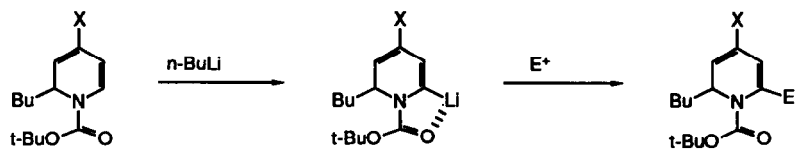
There has been considerable interest in 1-acyl-1,2-dihydropyridines as intermediates for the synthesis of substituted pyridines[1,2] and natural products.[1,3] These relatively stable 1,2-dihydropyridines are generally prepared by the addition of an organometallic[1-3] or reducing agent[4,5] to a 1-acylpyridinium salt. Frequently substituents on the pyridine ring cause the nucleophile to add non-regioselectively, or interfere with formation of the intermediate 1-acylpyridinium salt. As part of a program directed at substitution of 1-acyldihydropyridines in a regiospecific manner, we investigated the α-lithiation of 1-(tert-butoxycarbonyl)-1,2-dihydropyridines.[6]

Addition of n-butylmagnesium chloride to the 1-phenoxycarbonyl salt (**1**) of 4-chloropyridine, or 4-picoline, gave the 1,2-dihydropyridine **2** in good yield.[7] Treatment of **2** with potassium tert-butoxide



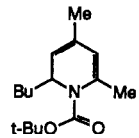
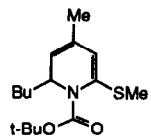
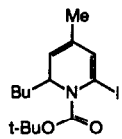
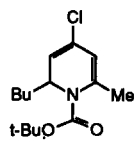
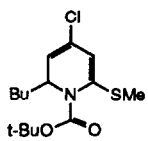
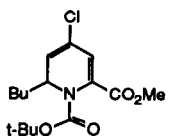
1 X = Me , Cl **2** **3**

in THF afforded the N-BOC derivative **3** in high yield. Metalation of **3** with 1.1 equiv of n-BuLi in THF at -42°C for 1h gave the α-lithiated 1,2-dihydropyridine **4**, which was treated with various electrophiles to give 2,4,6-trisubstituted 1,2-dihydropyridines **5** in high yield as shown in the table.



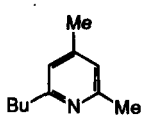
3 **4** **5**

Table. Reaction of α-Lithiated 1,2-Dihydropyridines **4** with Electrophiles

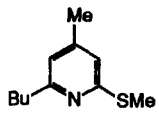
Entry[a]	X	Electrophile	Product[b]	Yield[c]
a	Me	MeI		85%
b	Me	MeSSMe		88%
c	Me	I_2		85%
d	Cl	MeI		81%
e	Cl	MeSSMe		86%
f	Cl	$MeOCO_2Me$		81%

[a]Reactions were performed on a 2-mmol scale in 6 ml of THF. The workup consisted of quenching with water 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 elemental analysis. [c]Yields are for isolated, pure material obtained from radial preparative layer chromatography (silica gel, ethyl acetate/hexanes).

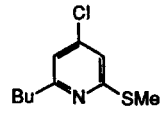
Aromatization of dihydropyridines **5** gives 2,4,6-trisubstituted pyridines **6**. Treatment of **5a**, **5b**, and **5e** with o-chloranil in toluene/acetic acid gave 2-butyl-4,6-dimethylpyridine (**6a**), 2-butyl-4-methyl-6-methylthiopyridine (**6b**) and 2-butyl-4-chloro-6-methylthiopyridine (**6e**) in 65, 44, and 63% yields, respectively.



6a

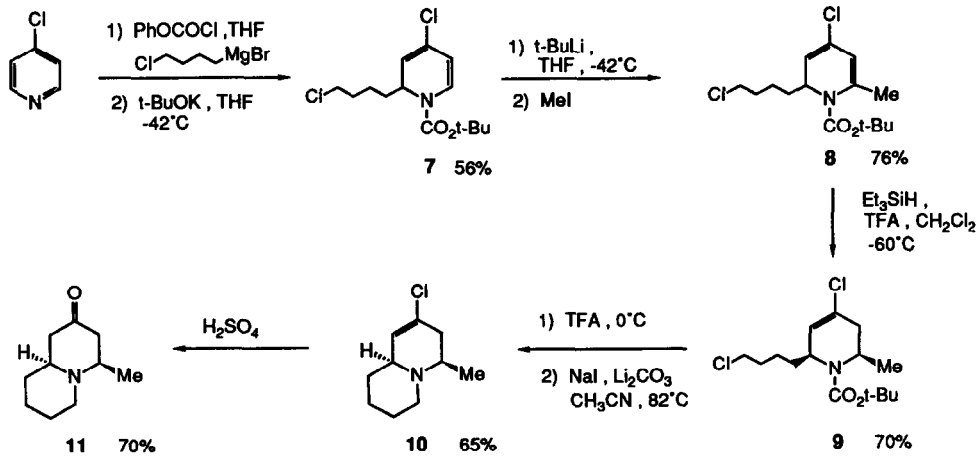


6b



6e

The α-metalation methodology was utilized in a synthesis of the quinolizidine alkaloid, (+)-epi-myrtine (**11**). The 1,2-dihydropyridine **7** was prepared from the reaction of 4-chloropyridine, phenyl chloroformate, and 4-chlorobutylmagnesium bromide,[8] followed by treatment of the crude product with potassium tert-butoxide in THF. Metalation with tert-butyllithium (THF, -42°C, 1h) and reaction with methyl iodide afforded 1,2-dihydropyridine **8** in good yield.[9] Reduction with triethylsilane in trifluoroacetic acid/methylene chloride at -42°C gave the cis-tetrahydropyridine **9** as the major product along with the trans- diastereomer in a ratio of 8 to 1.[10,11] Removal of the N-BOC group with trifluoroacetic acid followed by treatment of the resulting amine with NaI and Li_2CO_3 in refluxing acetonitrile afforded the quinolizidine **10** in 65% yield. Conversion of **10** to (+)-epi-myrtine (**11**) occurred on treatment with concentrated H_2SO_4 at room temperature. This product was identical to an authentic sample prepared by a literature procedure.[3c,12,13]



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9. In contrast to all other examples studied, n-butyllithium was ineffective at α-lithiating dihydropyridine 7.
10. The factors affecting the stereoselectivity of this reduction are under study.
11. Sodium borohydride and trifluoroacetic acid in benzene reduces the 5,6-double bond of 3-ethyl-N-(methoxycarbonyl)-1,2-dihydropyridine. M. J. Wyle and F. W. Fowler, J. Org. Chem., **49**, 4025 (1984).
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13. Spectral data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.4-3.2 (m, 1H), 2.5-2.0 (m, 6H), 1.9-1.5 (m, 5H), 1.5-1.25 (m, 2H), 1.2 (d, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.3, 61.9, 59.2, 50.9, 49.1, 48.7, 34.1, 25.8, 23.9, 20.7; IR (Neat) 2965, 2930, 2855, 2790, 2751, 1720, 1445, 1380, 1340, 1325, 1285, 1170, 1145, 1110, 1080, 1045, 990, 745 cm^{-1}; MS, M^+ 167.

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