Tetrahedron Letters,Vol.30,No.38,pp 5053-5056,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

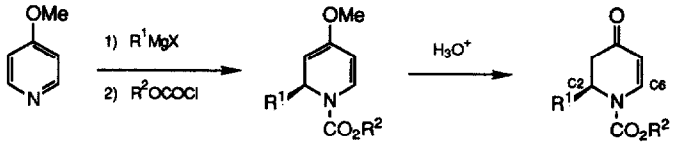
PREPARATION OF 1-(*TERT*-BUTOXYCARBONYL)-2,6-DIALKYL-2,3-DIHYDRO-4-PYRIDONES. A STEREOCONTROLLED SYNTHESIS OF (±)-MYRTINE.

Daniel L. Comins*‡ and Donald H. LaMunyon

Department of Chemistry, North Carolina State University
Raleigh, NC 27695-8204 and Department of Chemistry
and Biochemistry, Utah State University, Logan, UT 84322-0300

Summary: *A convenient preparation of N-BOC-2,6-dialkyl-2,3-dihydro-4-pyridones is described and utilized in a stereocontrolled synthesis of (±)-myrtine.*

We have recently been exploring a strategy for the synthesis of piperidine and quinolizidine alkaloids via 1-acyldihydropyridine intermediates.[1] The required dihydropyridines are conveniently prepared by the addition of Grignard regents to 1-acylpyridinium salts.[2,3] When 4-methoxypyridine (**1**) is used to form the 1-acylpyridinium salt, reaction with a Grignard reagent and workup with aqueous acid provides 2-alkyl-2,3-dihydro-4-pyridones **3** via 4-methoxydihydropyridines **2**.[1e]

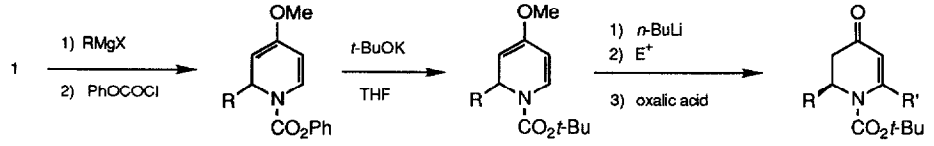


1 **2** **3**

The considerable A(1,3) strain between the C-2 substituent and the N-acyl group of **3** forces the C-2 group into the axial position.[4] Our synthetic strategy is designed to take advantage of this inherent conformational bias by using the stereocenter at C-2 to control the stereochemistry of carbon-carbon bond formation at C-6. Previously we studied the copper-mediated addition of Grignard reagents to 1-acyldihydropyridones similar to **3** and found the addition occurred stereoselectively to give *cis* 2,6-disubstituted piperidin-4-ones.[1e,j] This stereoselective axial attack at C-6 suggested an analogous route to *trans* 2,6-disubstituted piperidin-4-ones was feasible via copper hydride 1,4-addition to 2,6-disubstituted dihydropyridones **4**.

4 **5**

In order to test this strategy, a convenient preparation of enones 4 was needed. A three-step synthesis was developed from 4-methoxypyridine as shown below. A Grignard reagent, 4-methoxypyridine (**1**), and phenyl chloroformate gave 4-methoxy-1,2-dihydropyridines **6**, which on treatment with potassium *tert*-butoxide in THF gave the N-Boc derivatives **7**. Lithiation[5] with *n*-butyllithium (1.2 eq, THF, -42°C, 1h), reaction with electrophiles, and workup with aqueous oxalic acid gave the desired dihydropyridones **8** in good yield as shown in Table I.



6 **7** **8**

Table I. Synthesis of Dihydropyridones **8** from **7**.

dihydropyridine [a] **7**	R	E	R′	yield, [b,c] **8**, %
7a	Me	MeSSMe (3 equiv)	SMe	82[d]
7a	Me	I_2 (1 equiv)	I	83
7a	Me	*n*-BuI (6 equiv)	*n*-Bu	65
7a	Me	MeI (3 equiv)	Me	83[e]
7b	$Cl(CH_2)_4$-	MeSSMe (3 equiv)	SMe	77
7b	$Cl(CH_2)_4$-	MeI (3 equiv)	Me	58

[a] Reactions were generally performed on a 1-2 mmol scale. [b] Yields are for isolated, pure material obtained from radial PLC (silica gel, acetone/hexanes). [c] All products gave the expected IR, ^1H and ^{13}C NMR spectra and elemental analysis. Unless indicated, product was isolated as an oil. [d] mp 94.5-96.5°C (hexanes). [e] mp 35-39°C; This solid was not recrystallized but was purified by Kugelrohr distillation (bp 100-120°C/1.0 mm).

The above dihydropyridone preparation was utilized in a synthesis of the quinolizidine alkaloid, (±)-myrtine (**11**). Dihydropyridine **7a** was lithiated with *n*-butyllithium (1.2 eq, THF, -42°C, 1h) and alkylated with 1-chloro-4-iodobutane (6.0 equiv) to give dihydropyridone **9** (80%) on workup with aqueous oxalic acid. At this point the synthetic plan called for a stereoselective 1,4-reduction of the enone **9**. After examining several known reducing agents (see Table II), a highly stereoselective reduction was achieved using a copper hydride/BF_3·OEt_2 complex (entry g). The copper hydride was prepared from $LiAlH_2(OMe)_2$ and CuBr·SMe_2 (2:1) in THF (0°C, 30 min)[6] and treated with BF_3·OEt_2 (1 eq, -23°C, 20 min). Enone 9, complexed with 2 equiv of BF_3·OEt_2, was added to the copper hydride complex (-91°C) to give crude piperidones **10a** and **10b** in a ratio of 95:5. Pure **10a** was isolated in 56% yield by radial PLC (silica gel, 20% EtOAc/hexanes, 1% MeOH) and converted to (±)-myrtine[7,8] in 87% yield on treatment with TFA (0°, 1h) followed by aqueous $NaHCO_3$ (RT, 6h). This work represents a new approach to *trans*-2,6-dialkylpiperidones. The basic strategy should be amenable to the synthesis of a number of quinolizidine, indolizidine, and piperidine alkaloids.

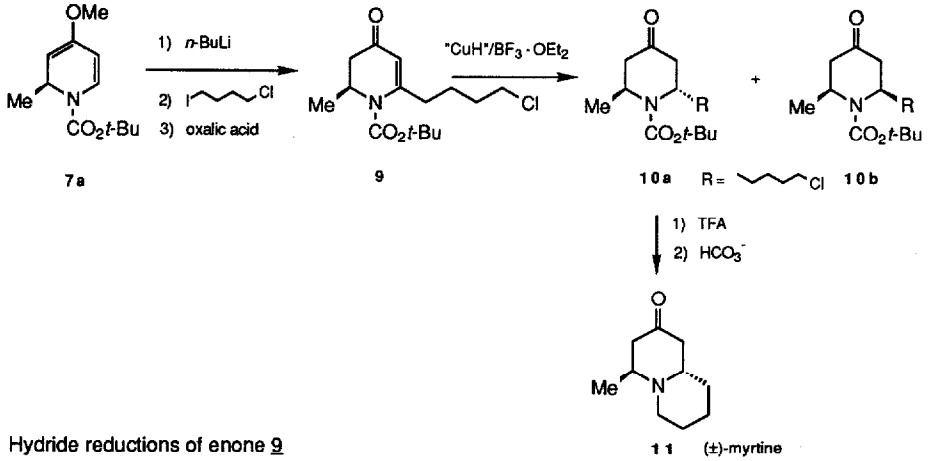


Table II. Hydride reductions of enone 9

entry	reaction conditions [a]	yield[b] of 10a and 10b	ratio[c] of *trans/cis* 10a/10b
a	2 equiv Ph_3SnH, $PhCH_3$, reflux, 21h	50	10:90
b	1 equiv L-Selectride[e], THF, -78°C, 1h	- 1,2-reduction (89%) -	
c	1) MAD[g] 2) 2 equiv L-Selectride[e], -78°C, 30 min	100	50:50
d	1) MAD[g] 2) 2 equiv Superhydride[f], -78°C, 30 min	97	50:50
e	1) 1.2 equiv BF_3·OEt_2 THF, -78°C 2) 1.2 equiv Superhydride[f], -78°C, 30 min; -23°C, 40 min	100[d]	65:35
f	1) 1.2 equiv BF_3·OEt_2, THF, -78°C 2) 2 $LiAlH(OCH_3)_3$ + CuBr -78°C, 10 min; -23°C, 1h	0[h]	
g	1) 2.05 equiv BF_3·OEt_2, THF, -78°C 2) 2 $LiAlH_2(OCH_3)_2$ + CuBr/BF_3·OEt_2 -91°C, 4h; -78°C, 1h	97[d]	95:5 [i]

[a] Reactions were generally performed on 0.3 to 1.0 mmol scale. [b] Yields are for isolated products obtained from radial PLC (silica gel, EtOAc/hexanes). [c] The *trans:cis* ratios were determined by 300-MHz ^1H NMR. [d] Yield is for crude product. [e] Lithium tri-*sec*-butylborohydride (Aldrich). [f] Lithium triethylborohydride (Aldrich). [g] Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide; see ref 9. [h] Starting material was recovered. [i] Ratio determined by GC.

Acknowledgment. We wish to express appreciation to the National Institutes of Health for support of this research. 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

‡ Address correspondence to this author at Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204.

1. (a) Comins, D.L.; Abdullah, A.H.; Smith, R.K. Tetrahedron Lett. **1983**, 24, 2711. (b) Comins, D.L.; Abdullah, A.H.; Mantlo, N.B. Tetrahedron Lett. **1984**, 25, 4867. (c) Comins, D.L.; Abdullah, A.H. Tetrahedron Lett. **1985**, 26, 43. (d) Comins, D.L.; Brown, J.D. Tetrahedron Lett. **1986**, 27, 2219. (e) Comins, D.L.; Brown, J.D. Tetrahedron Lett. **1986**, 27, 4549. (f) Comins, D.L.; Mantlo, N.B. J. Org. Chem. **1986**, 51, 5456. (g) Comins, D.L.; O'Connor, S. Tetrahedron Lett. **1987**, 28, 1843. (h) Comins, D.L.; Weglarz, M.A.; O'Connor, S. Tetrahedron Lett. **1988**, 29, 1751. (i) Comins, D.L.; Weglarz, M.A. J. Org. Chem. **1988**, 53, 4437. (j) Brown, J.D.; Foley, M.A.; Comins, D.L. J. Am. Chem. Soc. **1988**, 110, 7445. (k) Comins, D.L.; Foley, M.A. Tetrahedron Lett. **1988**, 29, 6711.

2. For reviews on dihydropyridines, see: Stout, D.M.; Meyers, A.I. Chem. Rev. **1982**, 82, 223. Sausins, A.; Duburs, G. Heterocycles **1988**, 27, 291. Comins, D.L.; O'Connor, S. Adv. Heterocycl. Chem. **1988**, 44, 199.

3. Comins, D.L.; Abdullah, A.H. J. Org. Chem. **1982**, 47, 4315. Comins, D.L.; Mantlo, N.B. J. Heterocycl. Chem. **1983**, 20, 1239. Comins, D.L.; Stroud, E.; Herrick, J.J. Heterocycles **1984**, 22, 151. Comins, D.L.; Mantlo, N.B. J. Org. Chem. **1985**, 50, 4410. Comins, D.L.; Mantlo, N.B. Tetrahedron Lett. **1987**, 28, 759.

4. 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. Beak, P.; Zajdel, W.J. J. Am. Chem. Soc. **1984**, 106, 1010 and references therein.

5. The α-lithiation of 1-(*tert*-butoxycarbonyl)-1,2- and 1,4-dihydropyridines has been reported: Comins, D.L. Tetrahedron Lett. **1983**, 24, 2807; refs 1 i,j. For a review on the metalation of amine derivatives adjacent to nitrogen, see: Beak, P.; Zajdel, W.J.; Retiz, D.B. Chem. Rev. **1984**, 84, 471.

6. This copper hydride preparation is a modification of Semmelhack's procedure, which uses $LiAlH(OMe)_3$ and CuBr. Semmelhack, M.F.; Stauffer, R.D.; Yamashita, A. J. Org. Chem. **1977**, 42, 3180.

7. For other syntheses of (±)-myrtine, see: (a) Slosse, P.; Hootelé, C. Tetrahedron Lett. **1979**, 20, 4587; Tetrahedron **1981**, 37, 4287. (b) King, F.D. Tetrahedron Lett. **1983**, 24, 3281; King, F.D. J. Chem. Soc., Perkin Trans I **1986**, 447.

8. Spectral data for **11**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.39 (dt, 1H, J = 3 Hz and 6 Hz), 2.95-2.74 (m, 2H), 2.74-2.60 (m, 1H), 2.49 (dt, 1H, J = 3 Hz and 12 Hz), 2.37-2.20 (m, 2H, J = 12 Hz), 1.90-1.50 (m, 4H), 1.45-1.10 (m, 3H), 0.97 (d, 3H, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 57.0, 53.4, 51.3, 48.6, 48.0, 34.2, 25.8, 23.3, 11.0; IR (neat) 2937, 2859, 2815, 1721, 1441, 1375, 1335, 1288, 1240, 1173, 1114, 876, 840, 724 cm^{-1}; picrate mp 194-195°C (lit[7a] mp 190-192°C).

9. Maruoka, K.; Katsumasa, N.; Yamamoto, H. Tetrahedron Lett. **1987**, 28, 5723.

(Received in USA 7 July 1989)