following measurements were obtained on the freshly prepared sample: ^1H NMR and ^{13}C NMR spectra are discussed in the text; high-resolution mass spectrum. Calcd for $C_{15}H_{34}NOP$ m/e 275.2378, found m/e 275.2339.

On being allowed stand at room temperature, the product decomposed largely to tri-*n*-butylphosphine oxide.

Preparation of Azetidine from 3b. The above freshly distilled oil **3b** (4.53 g, 0.0164 mol) was heated at 190 °C for 1.5 h and the distallate collected by cooling in dry ice. The distillate (270 mg, 29% yield) was identified as azetidine by ^1H NMR and was shown to be 98% pure by GC and free of ethanol.

When the crude undistilled oil **3b** was used above, the final product, azetidine, contained some ethanol.

Registry No. 2, 72320-38-8; **3a**, 78064-88-7; **3b**, 78064-89-8; acrolein, 107-02-8; triphenylphosphine, 603-35-0; azetidine, 503-29-7; tri-*n*-butylphosphine, 998-40-3.

Supplementary Material Available: Tables of final crystallographic results on **3a**, consisting of atomic coordinates (also deposited with the Cambridge Data Base[12]), anisotropic thermal parameters, and generated hydrogen coordinates (3 pages). Ordering information is given on any current masthead page.

Regioselective Metalation of the 4-Position of Pyridine. New and Convenient Alkylation and Acylation of 3-Amino-5-methoxypyridine

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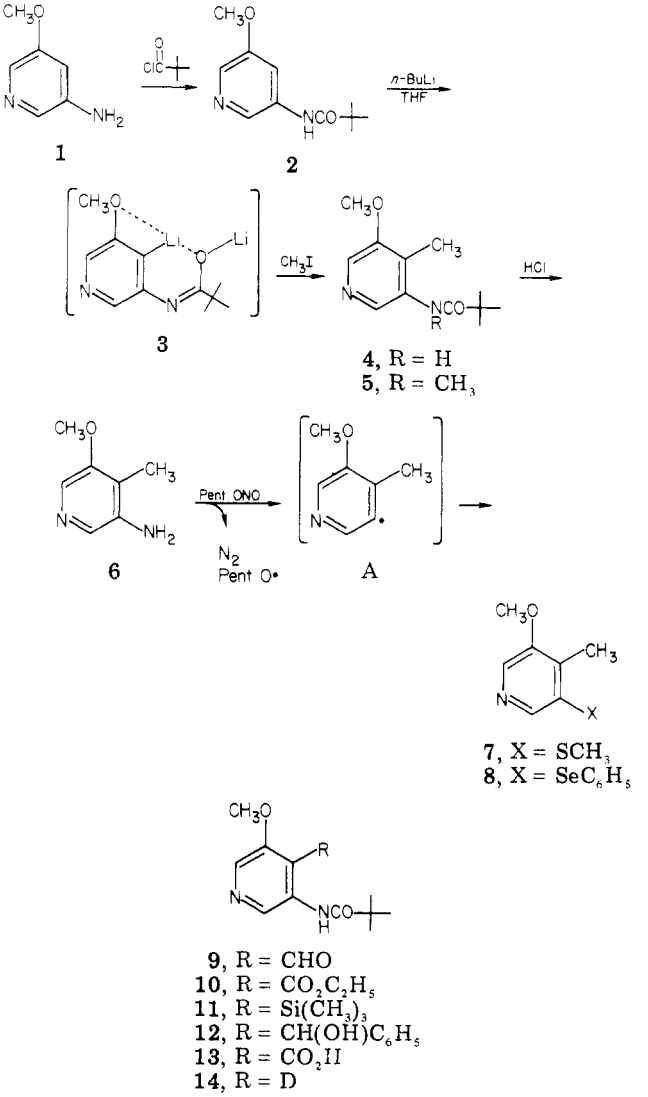
Prior to the work of Meyers[1,2] using the oxazoline functionality as an activating group, the direct metalation of pyridine was limited to a few examples.[3,4] The Meyers method gives a regioselective metalation of the 3-position of 4-(4,4-dimethyloxazolinyl-2-yl)pyridine by methyllithium and the 4-position of 3-(4,4-dimethyloxazolinyl-2-yl)pyridine by lithium amide. Very recently, regioselective lithiation of ethyl esters of nicotinic and isonicotinic acids,[5] halopyridines,[6] and *N,N*-diisopropylpyridylcarboxylic amides by lithium amide has been reported.[7] These results prompted us to publish our own results on the regioselective and direct ortho lithiation of 3-methoxy-5-(pivaloylamino)pyridine by *n*-butyllithium which affords 4-functionalized pyridine derivatives. Thus, 3-amino-5-methoxypyridine (**1**), readily obtained by a three-step sequence starting with 3,5-dibromopyridine *N*-oxide,[8] was transformed into the *N*-pivaloyl derivative (**2**) and was reacted with an excess of *n*-butyllithium to give the 4-lithio derivative (**3**). 3-Methoxy-5-(pivaloylamino)-4-methylpyridine (**4**) was isolated from the reaction mixture by quenching with methyl iodide. Optimization of the reaction conditions for the formation of **4** showed that the best yield (99% overall yield from **2**) was obtained when metalation was performed with 2.5 equiv of *n*-butyllithium at −25 °C for 1 h and the formed lithio derivative (**3**) was quenched with 4 equiv of methyl iodide at −70 °C. No 3-methoxy-4-methyl-5-(*N*-methylpivaloylamino)pyridine (**5**) was formed, although this substance could be prepared when the reaction was quenched with 4 equiv of methyl iodide at 0 °C. The combined activating effect toward alkyllithium by both *N*-pivaloylamino and methoxy groups ("coordination only" mechanism)[9] is

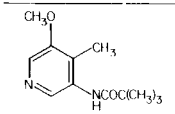
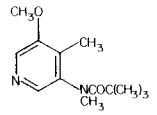
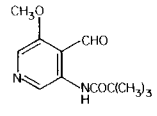
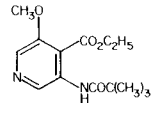
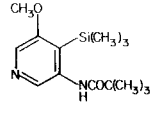
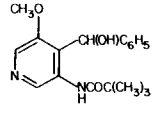
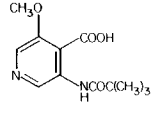
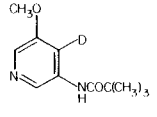
Scheme I



(1) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227.
(2) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133.
(3) The organolithium reagents usually add across the C=N bond of pyridines: Wakefield, B. J., "The Chemistry of Organolithium Compounds"; Pergamon Press: Elmsford, NY, 1974; pp 112–116. Therefore, lithiated pyridines have been obtained by halogen–metal exchange reactions of bromopyridines: Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485; Wibaut, J. P. de Jonge, A. P.; van der Voort, H. G. P.; Otto, P. Ph. H. L. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 1054; Murray, A., III; Foreman, W. W.; Langham, W. *J. Am. Chem. Soc.* **1948**, *70*, 1037; Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
(4) The metalation of the 4-position in 2,3,5,6-tetrachloropyridine and 2,3,6-trichloropyridine has been reported: Cook, J. D.; Wakefield, B. J. *J. Chem. Soc. C* **1969**, 1973.
(5) Ferles, M.; Silhánová, A. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3137.
(6) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.
(7) Epsztajn, J.; Berski, Z.; Brzeziński, J. Z.; Jóźwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739.
(8) A facile preparation of the starting compound (**1**) is as follows. Refluxing a methanolic solution of 3,5-dibromopyridine *N*-oxide and KOH for 30 min gave a 79% yield of 3-bromo-5-methoxypyridine *N*-oxide [mp 200–210 °C (recrystallized from methanol); ν_{max} 1580, 1550, 1410 cm^{-1}], which was converted to 3-amino-5-methoxypyridine *N*-oxide [syrup; 95%; ν_{max} 1640, 1605, 1565, 1210 cm^{-1}; m/e 140 (M^+)] by treatment with aqueous ammonia–$CuSO_4$ in a sealed tube at 130 °C for 5 h. Deoxygenation of the oxide by the catalytic hydrogenation on Raney Ni in methanol at room temperature for 1 h gave a 95% yield of **1** [mp 54–55 °C (recrystallized from benzene); bp 185 °C (18 mmHg) [lit.[12] bp 166–168 °C (15 mmHg)]]; see: Tamura, Y.; Fujita, M.; Chen, L. C.; Kiyokawa, H.; Ueno, K.; Kita, Y. *Heterocycles* **1981**, *15*, 871.
(9) For a review of ortho lithiations, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360; Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133; Marburg, S.; Tolman, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1333.

0022-3263/81/1946-3563$01.25/0

Table I. Ortho Functionalization of 3-Methoxy-5-(pivaloylamino)pyridine

electrophile	product	reaction time, h (temp, °C)	% yield	mp,[a] °C (recryst solvent) [bp,[a] °C (torr)]	IR,[b] cm^{-1}	NMR,[c] δ
CH_3I	 **4**	0.5 (−70)	99	136–137 (ethyl acetate–*n*-hexane)	1680, 1575, 1425, 1280	1.34 (s, 9 H, *t*-Bu), 2.09 (s, 3 H, $ArCH_3$), 3.91 (s, 3 H, OCH_3), 8.05 (s, 1 H, Ar H), 8.51 (s, 1 H, Ar H)
	 **5**	0.5 (−70), 2 (0)	23	[205 (3)[d]]	1620, 1570, 1420, 1280	1.05 (s, 9 H, *t*-Bu), 2.14 (s, 3 H, Ar CH_3), 3.15 (s, 3, H, NCH_3), 3.96 (s, 3 H, OCH_3), 8.08 (br s, 2 H, Ar H)
$(CH_3)_2NCHO$	 **9**	0.5 (−70)	58	89–90 (*n*-hexane)	1680, 1665, 1600, 1560	1.36 (s, 9 H, *t*-Bu), 4.04 (s, 3 H, OCH_3), 8.23 (s, 2 H, Ar H), 9.77 (s, 1 H, CHO)
$C_2H_5CO_2Cl$	 **10**	0.5 (−70)	11	47–48 (*n*-hexane)	1720, 1680, 1580, 1555	1.32 (s, 9 H, *t*-Bu), 1.40 (t, 3 H, OCH_2CH_3), 3.96 (s, 3 H, OCH_3), 4.46 (q, 2 H, OCH_2CH_3), 8.18 (s, 1 H, Ar H), 9.36 (s, 1 H, Ar H)
$(CH_3)_3SiCl$	 **11**	0.3 (−70)	72	[230 (1)[d]]	1670, 1580, 1530, 1410	0.34 (s, 9 H, $SiMe_3$), 1.32 (s, 9 H, *t*-Bu), 3.85 (s, 3 H, OCH_3), 7.39 (br s, 1 H, NH), 8.02 (s, 1 H, Ar H), 8.42 (s, 1 H, Ar H)
C_6H_5CHO	 **12**	0.5 (−70)	81	188–190.5 (chloroform–*n*-hexane)	1660, 1585, 1560, 1410	1.29 (s, 9 H, *t*-Bu), 1.57 (br s, 1 H, OH), 3.89 (s, 3 H, OCH_3), 6.60 (s, 1 H, CH), 7.30 (s, 5 H, C_6H_5), 7.40 (br s, 1 H, NH), 8.04 (s, 1 H, Ar H), 9.24 (s, 1 H, Ar H)
CO_2	 **13**	1 (−70)	92	209–210 (water)	1700, 1665, 1605, 1565	1.19 (s, 9 H, *t*-Bu), 3.89 (s, 3 H, OCH_3), 8.27 (s, 1 H, Ar H), 8.43 (s, 1 H, Ar H), 9.38 (s, 1 H, OH)
D_2O	 **14**	1 (−25)	99	87–88 (ethyl acetate–*n*-hexane)	1680, 1590, 1575, 1510, 1455	1.33 (s, 9 H, *t*-Bu), 3.85 (s, 3 H, OCH_3), 7.47 (br s, 1 H, NH), 8.02 (br s, 2 H, Ar H)

[a] Uncorrected melting and boiling points are given. [b] Measured in $CHCl_3$. [c] Measured in $CDCl_3$ with internal Me_4Si. Pyridyl protons seen at low fields are probably due to the steric and shielding effects of the pyvaloylamido group in the 3-position. [d] Bath temperature.

sufficient to lead to an ortho lithiation of these pyridine derivatives, but activation of the pyridine nucleus by an *N*-pivaloylamino or methoxy group alone failed to give an ortho lithiation. Acid hydrolysis (10% HCl at 80 °C) of **4** gave a 90% yield of the 3-amino compound (**6**). A direct conversion of the 3-aminopyridine (**6**) to the 3-(methylthio)pyridine (**7**) and the 3-(phenylseleno)pyridine (**8**) was accomplished by using the pyridyl radical intermediate (A),[10] whereas an attempt using the diazonium salt failed to give **7** and **8**. Thus, the aminopyridine (**6**) was treated with isopentyl nitrite in dimethyl disulfide at 80 °C for 2 h to give a 61% yield of **7**. Replacement of dimethyl disulfide by diphenyl diselenide gave **8** in a 50% yield (Scheme I).

The scope of the reactivity of the 4-lithiated 3-methoxy-5-(pivaloylamino)pyridine (**3**) with various electrophiles such as *N*,*N*-dimethylformamide (DMF), ethyl chloroformate, trimethylsilyl chloride, benzaldehyde, carbon dioxide, and deuterium oxide was ascertained. In all the above reactions, no compound corresponding to metalation of any other positions could be isolated. The strucutres of these products (**2** and **4**–**14**) were proved by microanalyses and mass, IR, and ^{1}H NMR spectral data. The results are summarized in Table I.

The present method is quite useful for the functionalization of the 4-position of 3-methoxy-5-(pivaloylamino)-pyridine, since a wide range of functional groups can be incorporated regioselectively and the 3-amino group can be converted to other substituents via its radical intermediate (A) as observed in the reaction of **6**.

Experimental Section[11]

3-Methoxy-5-(pivaloylamino)pyridine (2). To an ice-cooled solution of **1**[8] (497 mg, 4 mmol) and triethylamine (607 mg) in chloroform (18 mL) was added a solution of pivaloyl chloride (531 mg, 4.4 mmol) in chloroform (2 mL) dropwise over 5 min with stirring. The reaction mixture was concentrated in vacuo and partitioned between saturated aqueous sodium bicarbonate (10 mL) and chloroform (200 mL). The organic layer was washed with saturated aqueous sodium chloride (20 mL), dried over magnesium sulfate, and evaporated in vacuo. The residual syrup was subjected to a column chromatography on silica gel with ethyl acetate as an eluting solvent to give the N-pivaloylated compound **2** (774 mg, 94%) as a solid. Recrystallization of a sample from ethyl acetate–*n*-hexane gave an analytical sample: mp 96 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (9 H, s, 3 CH_3), 3.84 (3 H, s, OCH_3), 7.4 (1 H, br s, NH), 8.03 (3 H, br s, Ar H); IR ($CHCl_3$) 3440, 1680, 1585, 1520 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.75; H, 13.45. Found: C, 63.69; H, 7.88; N, 13.42.

General Procedures for Lithiation of 3-Methoxy-5-(pivaloylamino)pyridine (2) and Reaction with Electrophiles. Typically, a 1.5 M solution of *n*-butyllithium in hexane (3.4 mL, 5 mmol) was added dropwise to a stirred solution of **2** (416 mg, 2 mmol) in anhydrous tetrahydrofuran (12 mL) at −25 °C under argon. Addition of the first equivalent of the lithium reagent gave a yellow colored solution; additional reagent resulted in white precipitates. After the reaction mixture was maintained for 1 h under the same conditions, it was cooled to −78 °C. This solution of **3** was then ready for use in subsequent reactions.

Except for the reaction of **3** with solid carbon dioxide, a solution of the appropriate electrophilic reagent in anhydrous tetrahydrofuran was added to a stirred solution of dianion **3** at −70 °C. (For the preparation of the isonicotinic acid derivative **13**, the dianion solution was added to a slurry of solid carbon dioxide in tetrahydrofuran.) The reaction mixture was stirred at the temperatures for the period indicated in Table I and it was partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. (For the synthesis of **13**, the reaction mixture was quenched with water and made neutral with 10% hydrochloric acid. The resulting solids were collected by filtration.) In many cases, the crude products obtained on removal of the solvent required purification by a column or preparative thin-layer chromatography on silica gel or alumina [e.g., compound **4**, silica gel (ethyl acetate–*n*-hexane 1:1); **11**, silica gel TLC (chloroform–ethyl acetate 2:1); **12**, preparative TLC, silica gel (ethyl acetate)].

3-Methoxy-4-methyl-5-(pivaloylamino)pyridine (4). This was prepared from **2** (416 mg, 2 mmol), *n*-BuLi (3.4 mL, 5 mmol), and MeI (0.5 mL, 8 mmol) in THF (15 mL).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.83; H, 8.16; N, 12.61. Found: C, 64.93; H, 8.31; N, 12.53.

3-Methoxy-4-methyl-5-(*N*-methylpivaloylamino)pyridine (5). This was prepared from **2** (416 mg, 2 mmol), *n*-BuLi (3.4 mL, 5 mmol), and MeI (0.5 mL, 8 mmol) in THF (15 mL); exact mass calcd for $C_{13}H_{20}N_2O_2$ 236.1526, found 236.1528.

4-Formyl-3-methoxy-5-(pivaloylamino)pyridine (9). This was prepared from **2** (1041 mg, 5 mmol), *n*-BuLi (8.5 mL, 12.5 mmol), and DMF (1.5 mL, 20 mmol) in THF (30 mL); exact mass calcd for $C_{12}H_{16}N_2O_3$ 236.1154, found 236.1156.

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.94; H, 6.82; N, 11.73.

4-(Carboethoxy)-3-methyl-5-(pivaloylamino)pyridine (10). This was prepared from **2** (106 mg, 0.5 mmol), *n*-BuLi (0.85 mL, 1.25 mmol), and $ClCO_2Et$ (0.048 mL, 0.5 mmol) in THF (4 mL); exact mass calcd for $C_{14}H_{20}N_2O_4$ 280.1424, found 280.1424.

3-Methoxy-5-(pivaloylamino)-4-(trimethylsilyl)pyridine (11). This was prepared from **2** (105 mg, 0.5 mmol), *n*-BuLi (0.85 mL, 1.25 mmol), and Me_3SiCl (218 mg, 2 mmol) in THF (6 mL); exact mass calcd for $C_{14}H_{24}N_2O_2Si$ 280.1604, found 280.1601.

3-Methoxy-α-phenyl-5-(pivaloylamino)-4-pyridylmethanol (12). This was prepared from **2** (105 mg, 0.5 mmol), *n*-BuLi (0.85 mL, 1.25 mmol), and benzaldehyde (53 mg, 0.5 mmol) in THF (5 mL).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.36; H, 7.02; N, 9.08.

3-Methoxy-5-(pivaloylamino)pyridine-4-carboxylic Acid (13). This was prepared from **2** (2083 mg, 10 mmol), *n*-BuLi (17 mL, 25 mmol), and solid carbon dioxide (5 g, 113 mmol) in THF (60 mL); exact mass calcd for $C_{12}H_{16}N_2O_4$ 252.1107, found 252.1105.

4-Deuterio-3-methoxy-5-(pivaloylamino)pyridine (14). This was prepared from **2** (106 mg, 0.5 mmol), *n*-BuLi (0.84 mL, 1.25 mmol), and D_2O (0.4 mL, 20 mmol) in THF (4 mL); exact mass calcd for $C_{12}H_{17}DN_2O_2$ 209.1271, found 209.1266.

3-Amino-5-methoxy-4-methylpyridine (6). A solution of compound **4** (452 mg, 1.83 mmol) in 10% aqueous hydrochloric acid (3 mL) was heated at 90 °C for 1 day. The aqueous solution was made basic by the addition of saturated aqueous sodium bicarbonate and concentrated in vacuo. Methanol was added to the residue and unsoluble materials were filtered off. The filtrate was evaporated in vacuo to give a solid, which was subjected to a column chromatography on alumina with ethyl acetate–methanol as eluting solvent to give the amino compound **6** (252 mg, 90%). Recrystallization from *n*-hexane gave an analytical sample: mp 73–74.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (3 H, s, CH_3), 3.0–3.8 (2 H, br s, NH_2), 3.87 (3 H, s, OCH_3), 7.7 (2 H, br s, Ar H); IR ($CHCl_3$) 3400, 2940, 1610, 1570, 1290 cm^{-1}.

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30, N, 20.28. Found: C, 60.93; H, 7.36; N, 20.05.

3-Methoxy-4-methyl-5-(methylthio)pyridine (7). A solution of isopentyl nitrite (commercially available from Aldrich Chemical Co. and Tokyo Chemical Industry Co.; 423.5 mg, 3.6 mmol) was added to a stirred solution of compound **6** (100 mg, 0.723 mmol) in dimethyl disulfide (1.02 g, 10.8 mmol) at 80 °C. A gas was evolved immediately and the mixture became deep brown. After complete gas evaluation, heating was continued at 80 °C for 1.5

(10) Giam, C. S.; Kikukawa, K. *J. Chem. Soc., Chem. Commun.* **1980**, 756. Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494. Butler, R. N. *Chem. Rev.* **1975**, *75*, 241.

(11) IR absorption spectra were recorded on a Hitachi EPI-G2 spectrometer, ^{1}H NMR spectra on a Hitachi R-20A spectrometer with tetramethylsilane as an internal standard, and mass spectra on a Hitachi RMU-6D mass spectrometer at 70 eV. High-resolution mass spectra were recorded on a JEOL-JMS D-300 mass spectrometer.

(12) Urban, R.; Schnider, O. *Helv. Chim. Acta* **1964**, *47*, 363.

h and the reaction mixture was concentrated to give a solid. Sublimation of the solid [70–80 °C (20 mmHg)] gave a 61% yield of 7: mp 61–63 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (3 H, s, CH_3), 2.50 (3 H, s, SCH_3), 3.91 (3 H, s, OCH_3), 7.6–8.7 (2 H, br s, 2 NCH); IR ($CHCl_3$) 1550, 1455, 1410, 1275, 1040 cm^{-1}.

Anal. Calcd for $C_8H_{11}NOS$: C, 56.78; H, 6.55; N, 8.28. Found: C, 56.68; H, 6.49; N, 8.36.

3-Methoxy-4-methyl-5-(phenylseleno)pyridine (8). A solution of isopentyl nitrite (140 mg, 1.36 mmol) was added to a stirred solution of **6** (42 mg, 0.34 mmol) in diphenyl diselenide (189 mg, 0.68 mmol) at 80 °C. Workup of the reaction mixture as described above gave a 50% yield of **8** as a syrup: bp 150 °C (2.5 mmHg) (bath temperature); ^{1}H NMR ($CDCl_3$) δ 2.31 (3 H, s, CH_3), 3.92 (3 H, s, OCH_3), 7.29 (5 H, s, C_6H_5), 8.13 (1 H, s, Ar H), 8.24 (1 H, s, ArH); IR ($CHCl_3$) 1570, 1540, 1460, 1400, 1280, 1190, 1025 cm^{-1}; exact mass calcd for $C_{13}H_{13}NOSe$ 279.0148 and 277.0174, found 279.0159 and 277.0171.

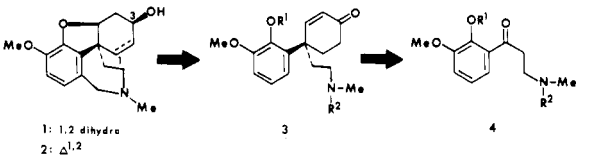
Registry No. 1, 64436-92-6; 2, 77903-25-4; 4, 77903-26-5; 5, 77903-27-6; 6, 77903-28-7; 7, 77903-29-8; 8, 77903-30-1; 9, 77903-31-2; 10, 77903-32-3; 11, 77903-33-4; 12, 77903-34-5; 13, 77903-35-6; 14, 77903-36-7; pivaloyl chloride, 3282-30-2; dimethyl disulfide, 624-92-0; diphenyl diselenide, 1666-13-3.

Communications

Total Synthesis of Racemic Lycoramine

Summary: The application of a general methodology for the construction of quaternary carbon atoms to the efficient total synthesis of the Amaryllidaceae alkaloid lycoramine (1) is described.

Sir: Inasmuch as the quaternary carbon atom is an important structural element found in numerous natural products, a variety of synthetic methods have been developed for the construction of such centers.[1] We have recently invented a general procedure for the formation of fully substituted carbon atoms by an efficient process that results in the net geminal acylation–alkylation of the carbonyl function of ketones.[2] In order to establish its practical utility, we report the successful implementation of this methodology as a key step in an efficient synthesis of lycoramine (1),[3] an Amaryllidaceae[4] alkaloid that is closely related to galanthamine (2).[5] The salient feature of our synthetic strategy is the preparation of a 4,4-disubstituted cyclohexenone such as **3**, which is suitably functionalized for elaboration to lycoramine (1), from a precursor ketone **4** by employing a new method for the annelation of a cyclohexenone ring at a carbonyl carbon atom.



After conducting a series of preliminary studies with several protected β-aminoethyl aryl ketones of type **4**, the *O*-allyl keto urethane **8** emerged as the starting material of choice. The preparation of **8** from commercially available *o*-vanillin (**5**) may be conveniently accomplished in 67% overall yield by a straightforward sequence of reactions. (See Scheme I.) Thus, alkylation of the sodium salt of *o*-vanillin with allyl bromide (2 equiv, DMF, 25 °C, 12 h) gave *O*-allyl-*o*-vanillin (**6**) (92%).[6] Addition of vinylmagnesium bromide (4 equiv, THF, 25 °C, 5 min) to **6** followed by Jones oxidation (0 °C, 30 min) of the intermediate alcohol afforded the α,β-unsaturated ketone **7** (81%). When **7** was allowed to react with benzyl *N*-methylcarbamate (1 equiv, 25 °C) in the presence of a catalytic amount (7%) of camphorsulfonic acid,[7] the requisite ketone **8** was produced (90%).

The next stage of the synthesis involves the transformation of **8** to the key intermediate cyclohexenone **11**, and our general procedure for introducing two dissimilar alkyl appendages at carbonyl carbon atoms via intermediate metalloenamines[2] seemed ideally suited to the task. In the event, sequential reaction of **8** with diethyl [(*N*-benzylidenamino)lithiomethyl]phosphonate (1.2 equiv, THF, −78 °C → reflux, 3 h) and *n*-butyllithium (1.2 equiv, THF, −78 °C, 1 h) provided the metalloenamine **9** which was treated in situ with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[8] (3 equiv, 20% HMPA–THF, −78 °C → 25 °C, 18 h) and then aqueous acid (1 N HCl, 6 h), yielding the intermediate δ-keto aldehyde **10**. When **10** was treated with base (0.5 N KOH, 30% aqueous MeOH, 25 °C, 2 h), facile cycloaldolization and dehydration ensued to give **11** in 40–45% overall yield from **8**.[9]

(1) For a review, see Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) Martin. S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.*, **1980**, *102*, 5866.

(3) For previous syntheses of lycoramine, see (a) Hazama, N.; Irie, H.; Mizutani, T.; Shingur, T.; Takada, M.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 2947. (b) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *Ibid.* **1968**, 2954. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065.

(4) For a review of the Amaryllidaceae alkaloids, see Funganti, C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New Yrok, 1975; Vol. 15, Chapter 3.

(5) For previous syntheses of galanthamine and related compounds, see (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Franck, B.; Lubs, H. J. *Justus Liebigs Ann. Chem.* **1968**, *720*, 131. (c) Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 2602. (d) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (e) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, R.; Hiiragi, M.; Hayasaka, T. *J. Chem. Soc. C* **1971**, 1043. (f) Kametani, T.; Yamaki, K.; Terui, T.; Shibuya, S.; Fukumoto, K. *Ibid.* **1972**, 1513. (g) Kametani, T.; Yamaki, K.; Terui, T. *J. Heterocycl. Chem.* **1973**, *10*, 35.

(6) The structure assigned to each compound was in accord with its spectral (^{1}H NMR, IR, mass) characteristics. Analytical samples of all new compounds were obtained by chromatography (HPLC) and gave satisfactory combustion analyses (C, H, N) and/or parent ion identification by high-resolution mass spectrometry. All yields are based upon isolated materials which were >95% pure.

(7) Cf. (a) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (b) Mohrle, H.; Engelsing, R. *Monatsh. Chem.* **1971**, *102*, 233.

(8) Brown, E.; Dhal, R. *Bull. Soc. Chim. Fr.* **1972**, 4292.

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