Chem. Pharm. Bull. 30(4)1257—1262(1982)

Synthetic Application of Lithiation Reactions: A Convenient Synthesis of 3,4-Dihydro-5-hydroxycarbostyril, 1,2,3,4-Tetrahydro-5-hydroxy-2-oxo-1,7-naphthyridine, and Methyl 3-Methoxypyridine-4-carboxylate

YASUMITSU TAMURA,* LING CHING CHEN, MASANOBU FUJITA, and YASUYUKI KITA

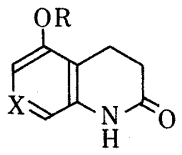
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka, Japan

(Received September 19, 1981)

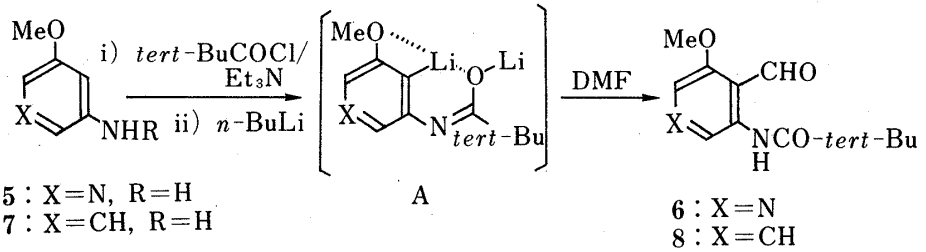
3,4-Dihydro-5-hydroxycarbostyril (**3**), a key intermediate for a clinically used β-receptor blocking agent (**1**), and its 7-aza analog (**4**) were prepared by an acid-catalyzed cyclization of the *N*-pivaloylamino-esters (**17** and **19**), which were obtained by using organolithiation of 3-methoxy-5-(pivaloylamino)pyridine and *m*-pivaloylanisidine, followed by Wittig and catalytic hydrogenation reactions. Some related pyridine derivatives (**15** and **24**) were also prepared.

Keywords——formylation of substituted pyridine and benzene derivatives; Wittig reaction of 4-formyl-3-methoxy-5-(pivaloylamino)pyridine and 2′-formyl-3′-methoxy-2,2-dimethylpropionanilide; acid-catalyzed lactam formation between ester and pivaloylamino groups; preparation of 1,7-naphthyridine and carbostyril nucleus; adrenergic receptor antagonist

Our interest in the synthesis of 5-(3-*tert*-butylamino-2-hydroxy)propoxy-3,4-dihydrocarbostyril (**1**, carteolol),[1] a clinically used β-receptor blocking agent,[2] and its 7-aza analog (**2**)[3] led us to seek a convenient route to the key intermediates, 3,4-dihydro-5-hydroxycarbostyril (**3**) and 1,2,3,4-tetrahydro-5-hydroxy-2-oxo-1,7-naphthyridine (**4**), respectively. Recently, we reported[4] the regioselective formylation of the 4-position of 3-amino-5-methoxypyridine (**5**)[5] by the heteroatom-facilitated lithiation of *N*-pivaloylated **5** followed by treatment with dimethylformamide, which affords a high yield of 4-formyl-3-methoxy-5-(pivaloylamino)-pyridine (**6**). We now found that *m*-anisidine (**7**) was also formylated at the 2-position to give 2′-formyl-3′-methoxy-2,2-dimethylpropionanilide (**8**) in high yield *via* the same lithiated intermediate (A).[6] These readily available bifunctional compounds (**6** and **8**) having amino



1 : X=CH, R=CH$_2$CH(OH)CH$_2$NH-*tert*-Bu
2 : X=N, R=CH$_2$CH(OH)CH$_2$NH-*tert*-Bu
3 : X=CH, R=H
4 : X=N, R=H



5 : X=N, R=H
7 : X=CH, R=H

A

6 : X=N
8 : X=CH

Fig. 1

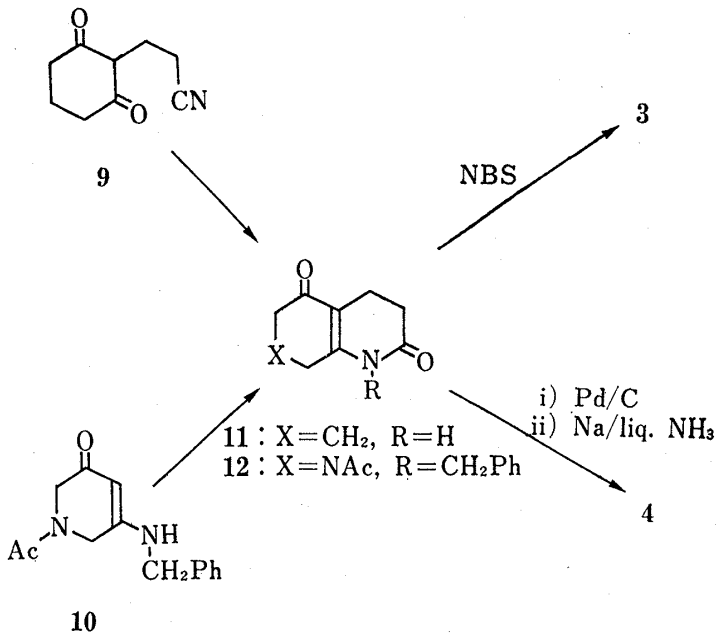


Chart 1

and formyl groups in an *ortho* position appeared to be attractive starting materials for the synthesis of **3** and **4**. These compounds (**3** and **4**) have been prepared by the intramolecular cyclization of cyclohexane-1,3-dione derivatives (**9** and **10**) to the bicyclic *N*-acyl-*β*-amino-vinylketones (**11** and **12**) followed by aromatization, as illustrated in Chart 1.[1,4] We now describe an alternative convenient synthesis of **3** and **4** *via* a Wittig reaction of the *ortho*-formylated compounds (**6** and **8**) using carboethoxymethylenetriphenylphosphorane, followed by reductive cyclization. The significant feature of the present method is the initial preparation of the aromatic amino-esters (**13** and **18**) prior to the cyclization into the bicyclic systems.

Results and Discussion

The starting formylated compounds (**6** and **8**) were prepared in high yield from **5** and **7**, respectively, by using the previously reported method.[4] Treatment of **6** with carboethoxymethylenetriphenylphosphorane in dry benzene at room temperature caused a Witting reaction to give a quantitative yield of the pyridine-4-propenoic ester (**13**) as a mixture of geometrical isomers. Heating of the mixture in hydrochloric acid without separation of each isomer gave a low yield of the cyclized compound (**14**) accompanied by decomposed materials. This may have occurred because the *E*-isomer is not easy to isomerize under the conditions used into the *z*-isomer, which is required for the cyclization. Demethylation of **14** was carried out with 48% hydrobromic acid to give 1,2-dihydro-5-hydroxy-2-oxo-1,7-naphthyridine(**15**). Unfortunately, these 1,2-dihydro-2-oxo-1,7-naphthyridines (**14** and **15**) failed to give the desired 1,2,3,4-tetrahydro-2-oxo-1,7-naphthyridines (**16** and **4**) in various catalytic hydrogenations. Since the difficulty of conversion of the unsaturated ester (**13**) into **16** or **4** appeared to be a result of the presence of the double bond, **13** was reduced to the saturated ester (**17**), which was readily cyclized to the naphthyridine (**16**) in hot hydrochloric acid. Demethylation of **16** was carried out in hot hydrobromic acid to give the desired naphthyridine (**4**).

Similarly, 2-formyl-*m*-anisidine (**8**) could be converted into the desired carbostyril (**3**). Wittig reaction of **8** with carboethoxymethylenetriphenylphosphorane gave a 77% yield of the unsaturated ester (**18**) as a geometrical mixture. Catalytic reduction of the mixture on Pd–C gave an 89% yield of the saturated ester (**19**), which was smoothly cyclized to the carbostyril (**20**). Demethylation of **20** to **3** with hot hydrobromic acid has been reported.[1]

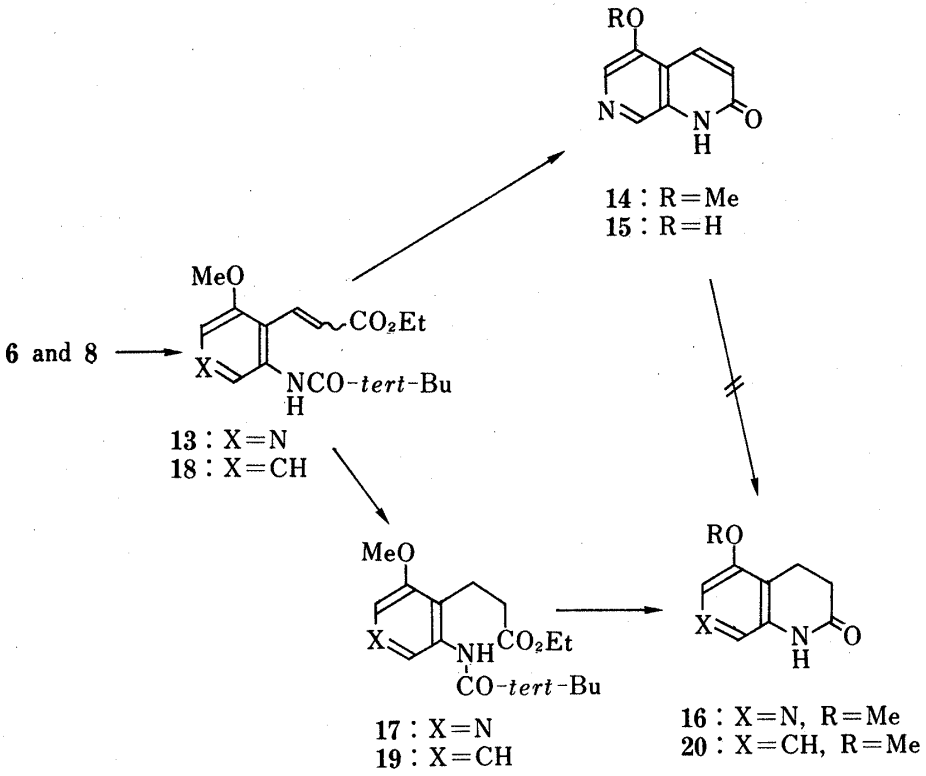


Chart 2

Next, we examined the synthesis of methyl 3-methoxypyridine-4-carboxylate (**24**) because of an interest in the chemistry of the pyridoxal analog[7] and the azacoumarine intermediate.[8] Reported methods[7-9] for the preparation of **24** involve drastic reaction conditions, many reaction steps, and/or poor overall yield. We now report an alternative short-step synthesis of **24** starting with 3-methoxy-5-(pivaloylamino)pyridine-4-carboxylic acid (**21**), as illustrated in Chart 3. Thus, the acid (**21**), readily obtained from **5** by the previously reported method,[4] was depivaloylated by heating with sodium hydroxide to give the amino acid (**22**), which was methylated in methanol–hydrochloric acid to give the amino-ester (**23**). Deamination of **23** to methyl 3-methoxypyridine-4-carboxylate (**24**) was carried out by treatment with isopentyl nitrite in dimethylformamide.[10] This series of reactions utilizing heteroatom-facilitated lithiation reactions could be a useful method for obtaining various bicyclic compounds (**14**—**16** and **20**) and 1,2,3-trisubstituted pyridine and benzene derivatives (**6**, **8**, **13**, **17**, **18**, **19**, and **21**—**23**).

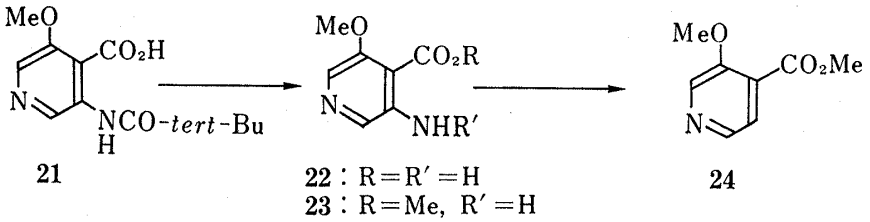


Chart 3

Experimental

All melting points are uncorrected. The infrared (IR) absorption spectra were recorded on a Shimadzu IR-27G spectrometer, and nuclear magnetic resonance (NMR) spectra on a Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were

obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Column chromatography was carried out on Merck Silicagel 60.

2′-Formyl-3′-methoxy-2,2-dimethylpropionanilide (8)——A 1.5 M solution of *n*-BuLi in hexane (3.28 ml, 4.82 mmol) was added dropwise to a solution of *m*-pivaloylanisidine[6] (400 mg, 1.93 mmol) in anhydrous tetrahydrofuran (THF) (15 ml) at 0°C under argon. After addition of the lithium reagent, the reaction mixture was maintained for 2 h under the same conditions. Dimethylformamide (DMF) (0.97 ml, 12.54 mmol) was added dropwise to the formed 4-lithio derivatives. The resulting mixture was stirred at 0°C for 1 h and at room temperature for 8 h and partitioned between ethyl acetate and water (15 ml). The organic phase was washed with sat. aqueous sodium chloride, dried over $MgSO_4$, and concentrated *in vacuo*. The residual solid was subjected to column chromatography on silica gel (with chloroform as the eluting solvent) to give a 73% yield (330 mg) of **8**. Recrystallization from *n*-hexane gave an analytical sample, mp 80—81°C. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.60; H, 7.35; N, 6.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3260, 1640, 1605, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.29 (9H, s, *tert*-Bu), 3.88 (3H, s, OCH_3), 6.45—8.5 (3H, m, ArH), 10.45 (1H, s, CH=O), 11.82 (1H, br s, NH).

Ethyl 3-(3-Methoxy-5-pivaloylamino-4-pyridyl)acrylate (13)——A solution of **6** (520 mg, 2.2 mmol) and carboethoxymethylenetriphenylphosphorane[11] (814 mg, 2.42 mmol) in dry benzene (20 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (with chloroform: ethyl acetate=1: 1 as the eluting solvent) to give a 97% yield (655 mg) of **13** as a mixture of *cis*- and *trans*-isomers (*cis*/*trans*=1/1). Recrystallization from ethyl acetate–*n*-hexane gave an analytical sample, mp 164—165°C. *Anal.* Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.74; H, 7.31; N, 9.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1680, 1550. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.25 (3×1/2H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and 9×1/2H, s, *tert*-Bu), 1.34 (3×1/2H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and 9×1/2H, s, *tert*-Bu), 3.95 (3H, s, OCH_3), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.1—7.7 (3H, m, –CH=CH– and NH), 8.17 (1H, br s, ArH), 8.61 (1H, br s, ArH). The mixture was used for the next reaction without separation of the isomers.

1,2-Dihydro-5-methoxy-2-oxo-1,7-naphthyridine (14)——A solution of **13** (600 mg, 1.96 mmol) in 10% aqueous hydrochloric acid (5 ml) was heated at 90°C for 1 h, then cooled to 0°C, and made basic by addition of sat. aqueous $NaHCO_3$. The mixture was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (with ethyl acetate: methanol=10: 1 as the eluting solvent) to give a 35% yield (120 mg) of **14**. Recrystallization from methanol gave an analytical sample, mp 274—276°C. *Anal.* Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.94; H, 4.59; N, 15.74. IR ν_{max}^{KCl} cm^{-1}: 1660, 1605, 1510. ^{1}H-NMR (10% solution in DMSO-d_6) δ: 3.95 (3H, s, OCH_3), 6.66 (1H, d, J=9.5 Hz, CH=C$\underline{H}$CO), 7.99 (1H, d, J=9.5 Hz, C$\underline{H}$=CHCO), 8.06 (1H, s, ArH), 8.32 (1H, s, ArH).

1,2-Dihydro-5-hydroxy-2-oxo-1,7-naphthyridine (15)——A solution of **14** (10 mg, 0.057 mmol) in 48% hydrobromic acid (1 ml) was refluxed for 4 h. The reaction mixture was concentrated *in vacuo* and neutralized by addition of 10% aqueous Na_2CO_3 to give a solid, which was purified by column chromatography on silica gel (with chloroform: methanol=7: 1 as the eluting solvent) to give a 44% yield (4 mg) of **15**, mp>300°C; IR ν_{max}^{KCl} cm^{-1}: 1660, 1610. ^{1}H-NMR (10% solution in DMSO-d_6) δ: 6.68 (1H, d, J=9.5 Hz, =CHCO), 7.92 (1H, s, ArH), 8.01 (1H, d, J=9.5 Hz, C$\underline{H}$=CHCO), 8.09 (1H, s, ArH). Exact mass calcd. for $C_8H_6N_2O_2$: 162.0426. Found: 162.0426.

Ethyl 3-(3-Methoxy-5-pivaloylamino-4-pyridyl)propionate (17)——A solution of **13** (50 mg, 0.16 mmol) in methanol (15 ml) was hydrogenated on 5% Pd–C (50 mg) at 4 atm pressure and room temperature for 1 h. After removal of Pd–C by filtration, the filtrate was concentrated *in vacuo* to give an 81% yield (40 mg) of **17** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 1700, 1660, 1580, 1560. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.37 (9H, s, *tert*-Bu), 2.77 (4H, s, CH_2×2), 3.91 (3H, s, OCH_3), 4.09 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 8.02 (1H, s, ArH), 8.58 (1H, s, ArH). Exact mass calcd. for $C_{16}H_{24}N_2O_4$: 308.1736. Found: 308.1738. This product was used for the next reaction without further purification.

1,2,3,4-Tetrahydro-5-methoxy-2-oxo-1,7-naphthyridine (16)——A solution of **17** (40 mg, 0.13 mmol) in 10% hydrochloric acid (2 ml) was heated at 90°C for 1 h. The reaction mixture was neutralized with sat. aqueous $NaHCO_3$ and the resulting crystals were collected by filtration. Recrystallization of the crystals from methanol gave a 47% yield (11 mg) of **16**, mp 276—278°C. *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.84; H, 4.98; N, 15.72. IR ν_{max}^{KCl} cm^{-1}: 1665, 1585. ^{1}H-NMR (10% solution in DMSO-d_6) δ: 2.25—2.65 (2H, m, $=CCH_2$), 2.6—3.0 (2H, m, CH_2CO), 3.88 (3H, s, OCH_3), 7.84 (1H, s, ArH), 7.96 (1H, s, ArH).

1,2,3,4-Tetrahydro-5-hydroxy-2-oxo-1,7-naphthyridine (4)——A solution of **16** (10 mg, 0.056 mmol) in 48% hydrobromic acid (1 ml) was refluxed for 4 h. The reaction mixture was concentrated *in vacuo* and neutralized by addition of 10% aqueous Na_2CO_3 to give a solid, which was purified by column chromatography on silica gel (with ethyl acetate: methanol=4: 1 as the eluting solvent) to give a 54% (5 mg) yield of **4**, which was identical with an authentic sample obtained by a different route.[3]

Ethyl (2-Methoxy-6-pivaloylamino)cinnamate (18)——A solution of **8** (250 mg, 1.06 mmol) and carboethoxymethylenetriphenylphosphorane[11] (393 mg, 1.17 mmol) in dry benzene (10 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (with ethyl acetate: chloroform=1: 1 as the eluting solvent) to give a 77%

yield (250 mg) of **18** as a mixture of *cis*- and *trans*-isomers (*cis*/*trans*=1/1). Recrystallization from ethyl acetate–*n*-hexane gave an analytical sample, mp 45—46°C. *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.58; H, 7.71; N, 4.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1715, 1700, 1670, 1625, 1600, 1585. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.22 (3×1/2H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and 9×1/2H, s, *tert*-Bu), 1.31 (3×1/2H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and 9×1/2H, s, *tert*-Bu), 1.67 (1H, s, NH), 3.79 (3×1/2H, s, OCH_3), 3.86 (3×1/2H, s, OCH_3), 4.12 (2×1/2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.25 (2×1/2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 6.0—8.2 (3H, m, ArH). The mixture was used for the next reaction without separation of the isomers.

2′-Ethoxycarbonylethyl-3′-methoxy-2,2-dimethylpropionanilide (**19**)——A solution of **18** (200 mg, 0.68 mmol) in ethanol (30 ml) was hydrogenated on 5% Pd–C (200 mg) at 4 atm pressure and room temperature for 1 h. After removal of Pd–C by filtration, the filtrate was concentrated *in vacuo* to give an 89% yield (180 mg) of **19** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1710, 1660, and 1590. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.18 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.35 (9H, s, *tert*-Bu), 2.77 (4H, s, CH_2×2), 3.80 (3H, s, OCH_3), 4.08 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 6.5—7.5 (3H, m, ArH), 9.08 (1H, br s, NH). Exact mass calcd. for $C_{17}H_{25}NO_4$: 307.1781. Found: 307.1770. This product was used for the next reaction without further purification.

3,4-Dihydro-5-methoxycarbostyril (**20**)——A solution of **19** (160 mg, 0.52 mmol) in 10% hydrochloric acid (3 ml) was heated at 90°C for 1 h. The reaction mixture was neutralized with sat. aqueous $NaHCO_3$ and extracted with chloroform. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residual solid was subjected to column chromatography on silica gel (with chloroform as the eluting solvent) to give a 43% yield (40 mg) of **20**, which was recrystallized from methanol to give a pure sample, mp 175—177°C (lit.[1] 175—177°C). This was identical with an authentic sample obtained by a different route.[1]

3-Amino-5-methoxypyridine-4-carboxylic Acid (**22**)——A solution of **21**[4] (1.5 g, 6 mmol) in 10% hydrochloric acid (5 ml) was heated at 90°C for 5 h. The aqueous solution was made basic by addition of sat. aqueous $NaHCO_3$ to give a solid, which was recrystallized from water to give a 62% yield (615 mg) of **22**. Recrystallization from water gave an analytical sample, mp 214—215°C. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.85; H, 4.75; N, 16.53. IR ν_{max}^{KCl} cm^{-1}: 3340, 3180, 1650, 1620, 1540. ^{1}H-NMR (10% solution in DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 7.55 (1H, s, ArH), 7.79 (1H, s, ArH).

Methyl 3-Amino-5-methoxypyridine-4-carboxylate (**23**)——Hydrogen chloride gas was bubbled through a solution of **22** (100 mg, 0.6 mmol) in dry methanol (3 ml) at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and partitioned between 28% aqueous ammonia and chloroform. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallized from acetone–*n*-hexane to give a 55% (60 mg) yield of **23**. Recrystallization from acetone–*n*-hexane gave an analytical sample, mp 79—80°C. *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.62; H, 5.72; N, 15.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3360, 1720, 1680, 1595, 1570. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.86 (6H, s, OCH_3 and CO_2CH_3), 5.13 (2H, br s, NH_2), 7.69 (1H, s, ArH), 7.81 (1H, s, ArH).

Methyl 3-Methoxypyridine-4-carboxylate (**24**)——A solution of isopentyl nitrite (commercially available from Aldrich Chemical Co. and Tokyo Chemical Industry Co.; 149 mg, 1.26 mmol) was added to a stirred solution of **23** (77 mg, 0.42 mmol) in dry DMF (1 ml) at 65°C. A gas was evolved immediately and the mixture was concentrated *in vacuo* to give a solid. The residue was subjected to column chromatography on silica gel (with ethyl acetate: *n*-hexane=1: 1 as the eluting solvent) to give a 30% yield (21 mg) of **24**, which was identical with an authentic specimen.[7]

Acknowledgement The authors acknowledge financial assistance of this work in the form of a Grant-in-Aid for Special Project Research (Grant No. 311704), "Chemical Research in Development and Utilization of Nitrogen-Organic Resources," from the Ministry of Education, Science and Culture, Japan.

References and Notes

1) Preparation of carteolol: see, K. Nakagawa, M. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuuchi, and S. Shintani, *J. Med. Chem.*, **19**, 529 (1974); Y. Tamura, K. Ozaki, K. Koyama, and K. Sumoto, *Yakugaku Zasshi*, **92**, 772 (1972); Y. Tamura, M. Terashima, Y. Higuchi, and K. Ozaki, *Chem. Ind.* (London), **1970**, 1435.
2) The drug has been sold by Otsuka Pharmaceutical Co. of Japan.
3) Recently, we prepared the 7-aza analog of carteolol starting with *N*-acetylpiperidine-3,5-dione: Y. Tamura, L.C. Chen, M. Fujita, H. Kiyokawa, and Y. Kita, *Chem. Pharm. Bull.*, **29**, 2460 (1981).
4) Y. Tamura, M. Fujita, L.C. Chen, M. Inoue, and Y. Kita, *J. Org. Chem.*, **46**, 3564 (1981).
5) A facile preparation of **5** has been established: Y. Tamura, M. Fujita, L.C. Chen, H. Kiyokawa, K. Ueno, and Y. Kita, *Heterocycles*, **15**, 871 (1981).
6) *ortho*-Lithiation of *m*-anisidine has been reported: W. Fuhrer and H.W. Gschwend, *J. Org. Chem.*, **44**, 1133 (1979); S. Marburg and R.L. Tolman, *J. Heterocycl. Chem.*, **17**, 1333 (1980).
7) D. Heinert and A.E. Martell, *Tetrahedron*, **3**, 49 (1958); *idem*, *J. Am. Chem. Soc.*, **81**, 3933 (1959); M.H. O'Leary and J.R. Payne, *J. Med. Chem.*, **14**, 773 (1971).
8) R.B. Moffett, *J. Org. Chem.*, **35**, 3596 (1970); T. Matsuo and T. Miki, *Chem. Pharm. Bull.*, **20**, 669, 806 (1972); J.-V. Dejardin and C.-L. Lapiere, *Bull. Soc. Chim. Fr.*, **1976**, 530; *idem*, *ibid.*, **1978**, 72.

9) H. Yamada and H. Tobiki, Japan. Kokai, Tokkyo Koho, 7905978 (1979) [*C.A.*, **91**, 39329*t* (1980)].
10) M.P. Doyle, J.F. Dellaria, Jr., B. Siegfried, and S.W. Bishop, *J. Org. Chem.*, **42**, 3494 (1977) and references cited therein.
11) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).