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

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3,4-Dihydro-5-hydroxycarbostryl (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 carbostryl nucleus; adrenergic receptor antagonist

Our interest in the synthesis of 5-(3-*tert*-butylamino-2-hydroxy)propoxy-3,4-dihydro-carbostryl (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-hydroxy-carbostryl (3) and 1,2,3,4-tetrahydro-5-hydroxy-2-oxo-1,7-naphthyridine (4), respectively. Recently, we reported⁴⁾ the regioselective formylation of the 4-position of 3-amino-5-methoxy-pyridine (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

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 Wittig 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 carbostyryl (**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 carbostyryl (**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 analog⁷⁾ and the azacoumarine intermediate.⁸⁾ Reported methods⁷⁻⁹⁾ 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*-pivaloylanisidine⁶⁾ (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 MgSO₄, 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 C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.60; H, 7.35; N, 6.14. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3260, 1640, 1605, 1580. ¹H-NMR (10% solution in CDCl₃) δ : 1.29 (9H, s, *tert*-Bu), 3.88 (3H, s, OCH₃), 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 carboethoxymethylenetriphenylphosphorane¹¹⁾ (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 C₁₆H₂₂N₂O₄: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.74; H, 7.31; N, 9.19. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1700, 1680, 1550. ¹H-NMR (10% solution in CDCl₃) δ : 1.25 (3×1/2H, t, *J*=7 Hz, CO₂CH₂CH₃ and 9×1/2H, s, *tert*-Bu), 1.34 (3×1/2H, t, *J*=7 Hz, CO₂CH₂CH₃ and 9×1/2H, s, *tert*-Bu), 3.95 (3H, s, OCH₃), 4.11 (2H, q, *J*=7 Hz, OCH₂CH₃), 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 NaHCO₃. 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 C₉H₈N₂O₂: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.94; H, 4.59; N, 15.74. IR $\nu_{\text{max}}^{\text{KCl}}$ cm⁻¹: 1660, 1605, 1510. ¹H-NMR (10% solution in DMSO-*d*₆) δ : 3.95 (3H, s, OCH₃), 6.66 (1H, d, *J*=9.5 Hz, CH=CHCO), 7.99 (1H, d, *J*=9.5 Hz, CH=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 Na₂CO₃ 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 $\nu_{\text{max}}^{\text{KCl}}$ cm⁻¹: 1660, 1610. ¹H-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, CH=CHCO), 8.09 (1H, s, ArH). Exact mass calcd. for C₈H₆N₂O₂: 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 $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3320, 1700, 1660, 1580, 1560. ¹H-NMR (10% solution in CDCl₃) δ : 1.20 (3H, t, *J*=7 Hz, OCH₂CH₃), 1.37 (9H, s, *tert*-Bu), 2.77 (4H, s, CH₂×2), 3.91 (3H, s, OCH₃), 4.09 (2H, q, *J*=7 Hz, OCH₂CH₃), 8.02 (1H, s, ArH), 8.58 (1H, s, ArH). Exact mass calcd. for C₁₆H₂₄N₂O₄: 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 NaHCO₃ 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 C₉H₁₀N₂O₂: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.84; H, 4.98; N, 15.72. IR $\nu_{\text{max}}^{\text{KCl}}$ cm⁻¹: 1665, 1585. ¹H-NMR (10% solution in DMSO-*d*₆) δ : 2.25–2.65 (2H, m, =CCH₂), 2.6–3.0 (2H, m, CH₂CO), 3.88 (3H, s, OCH₃), 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 Na₂CO₃ 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 carboethoxymethylenetriphenylphosphorane¹¹⁾ (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. 1H -NMR (10% solution in $CDCl_3$) δ : 1.22 (3 $\times$ 1/2H, t, J =7 Hz, $CO_2CH_2CH_3$ and 9 $\times$ 1/2H, s, *tert*-Bu), 1.31 (3 $\times$ 1/2H, t, J =7 Hz, $CO_2CH_2CH_3$ and 9 $\times$ 1/2H, s, *tert*-Bu), 1.67 (1H, s, NH), 3.79 (3 $\times$ 1/2H, s, OCH_3), 3.86 (3 $\times$ 1/2H, s, OCH_3), 4.12 (2 $\times$ 1/2H, q, J =7 Hz, $CO_2CH_2CH_3$), 4.25 (2 $\times$ 1/2H, q, J =7 Hz, $CO_2CH_2CH_3$), 6.0–8.2 (3H, m, ArH). The mixture was used for the next reaction without separation of the isomers.

2'-Ethoxycarbonyl-ethyl-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. 1H -NMR (10% solution in $CDCl_3$) δ : 1.18 (3H, t, J =7 Hz, $CO_2CH_2CH_3$), 1.35 (9H, s, *tert*-Bu), 2.77 (4H, s, $CH_2 \times 2$), 3.80 (3H, s, OCH_3), 4.08 (2H, q, J =7 Hz, $CO_2CH_2CH_3$), 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-methoxycarbostyryl (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 $\nu_{\max}^{KCl}$ cm^{-1} : 3340, 3180, 1650, 1620, 1540. 1H -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. 1H -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⁾

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