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SYNTHESIS OF NEW FRIEDLÄNDER SYNTHON AND ITS APPLICATION TOWARDS THE CONSTRUCTION OF PYRIDO[3,2-*c*]ACRIDINES

Jong Keun Son, Jae Keun Son, and Yurngdong Jahng*

College of Pharmacy, Yeungnam University, Kyongsan 712-749, Korea

Abstract - A new Friedländer synthon, 4-aminoacridine-3-carbaldehyde was prepared in 4 steps from 3-methylacridine in 38% overall yield, which was readily condensed with acetylaromatics to yield 2-arylpyrido[3,2-*c*]-acridines.

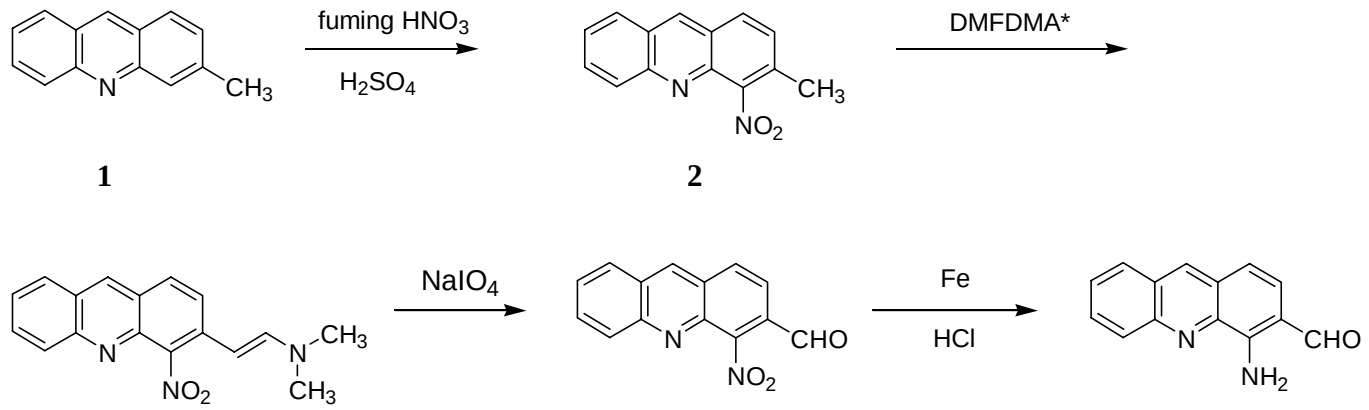
The increasing interests of pyrido-fused acridines, especially pyrido[3,2-*c*]acridine and related derivatives stem from their properties not only of showing broad spectrum of biological properties such as antileukemic,[1] antithrombic,[2] and anticancer activities,[3] but also of acting as ligands for complexation with small organic molecules[4] as well as transition metals.[5] Even such a variety of utility have been reported, general and efficient synthetic methods have not been established as yet.[6] The synthetic methods reported so far were limited to include the Skraup reaction of 4-aminoacridines[7] and the Friedel-Crafts reaction of 7-acyl-8-arylaminoquinolines.[8]

On the other hand, the Friedländer reaction,[9] a reaction of β-amino-α,β-unsaturated aldehydes or *ortho*-aminophenones with ketones containing methylene units α to the carbonyl groups, is one of the facile and efficient methods to construct quinoline and related nuclei in a variety of intriguing molecules such as biologically important molecules[10] and polydentate ligands.[11] Limited numbers of β-amino-α,β-unsaturated aldehydes as a Friedländer synthon have been only obstacle for the usage of such a reaction.

In connection with our interests in the design and synthesis of new polydentates and in the development of new synthetic methods for the preparation of cytotoxic heterocycles, we herein described the synthesis of 4-aminoacridine-3-carbaldehyde as a new Friedländer synthon which would have a general utility for the construction of pyrido[3,2-*c*]acridine.

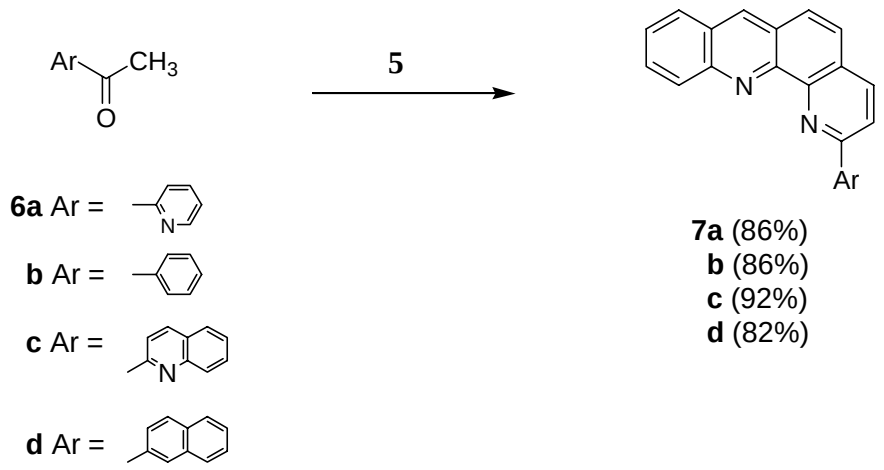
RESULTS AND DISCUSSION

The 3-methylacridine (**1**) was chosen as a starting material to which Thummel's 4-step procedure[12] for the preparation of 8-aminoquinoline-7-carbaldehyde was applied. The prerequisite 3-methyl-acridine was prepared from cyclohexanone in 4 steps by the method of Petrow.[13] Nitration of **1** with fuming HNO_3 in 98% H_2SO_4 afforded a 4-nitro compound (**2**) in 86% yield. Failure of direct oxidative conversion of methyl to formyl group by SeO_2 led alternative methods. The 3-methyl group was, thus converted to *trans*-*N*,*N*-dimethylaminoethenyl group by *trans*-*N*,*N*-dimethylform-amide dimethyl acetal (DMFDMA)[14] in 89% yield. The presence of two one-proton doublets at δ 7.18 and 5.16 with a coupling constant 13.3 Hz and disappearance of the methyl resonance confirmed the completion of reaction. Cleavage of the double bond by $NaIO_4$ provided the nitroaldehyde (**4**) in 70% yield. Conventional reduction of a nitro group by Fe in con. HCl afforded a desired aminoaldehyde (**5**) in 85% yield. ^{1}H NMR spectrum showed a one-proton singlet at δ 9.99 for CHO and seven well resolved one-proton resonances which were assigned by double-quantum filtered COSY experiments.



*DMFDMA = *N*,*N*-dimethylaminoformamide dimethyl acetal

The Friedländer condensation of **5** with a series of acetylaromatics (**6**) provided corresponding 2-arylpyrido[3,2-*c*]acridines (**7**) in 82-92% yield. In ^{1}H NMR spectra, compounds (**7**) showed characteristic proton resonances for H11 and H7 of acridine moiety at the region of δ 8.47-9.07 and δ 8.64-8.79 as one-proton doublets and one-proton singlets, respectively. The protons H5 and H6 were resonanced at the region of δ 8.24-7.22 as AB quartets as previously reported.[12]



In conclusion, a new Friedländer synthon, 4-aminoacridine-3-carbaldehyde (**5**) was prepared in 4 steps from 3-methylacridine in 39% overall yield. Friedländer condensation of **5** with a series of acetylaromatics afforded 2-arylpyrido[3,2-*c*]acridines (**7a-d**) in good yields.

EXPERIMENTAL

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 or 400 spectrometer 250 or 400 MHz for ^{1}H NMR and 62.5 or 100 MHz for ^{13}C as it was noted, and are reported as parts per million (ppm) from the internal standard TMS. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

4-Nitro-3-methylacridine (2)

A mixture of fuming HNO_3 (0.16 g) and 98% H_2SO_4 (10 mL) was slowly added to the solution of 0.5 g (2.6 mmol) of 3-methylacridine in 98% H_2SO_4 (20 mL) in an ice bath. The resulting mixture was stirred for 30 min, poured into finely crushed ice, and extracted with CH_2Cl_2 (20 mL x 3). The organic layer was dried over $MgSO_4$. Evaporation of the solvent under the reduced pressure afforded a solid material which was chromatographed on silica gel eluting with *n*-hexane:CH_2Cl_2 (1:1). The early fractions afforded 0.33 g (86%) of yellow needles after recrystallization from *n*-hexane:CH_2Cl_2(1:1): mp 183-184 °C. IR (KBr) υ 2817, 1620, 1525, 1378, 1315, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.79 (s, 1H, H9), 8.24 (d, *J* = 8.8 Hz, 1H, H5), 8.02 (d, *J* = 8.7 Hz, 1H),

8.01 (d, *J* = 8.2 Hz, 1H), 7.82 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H6), 7.56 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H7), 7.40 (d, *J* = 8.7 Hz, 1H), 2.62 (s, 3H). High resolution MS: 238.12. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 71.74; H, 4.27; N, 12.02.

3-(*trans*-*N*,*N*-Dimethylamionethenyl)-4-nitroacridine (**3**)

A mixture of **2** (0.20 g, 0.84 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.2 mL) in dry DMF (4 mL) was heated under N_2 at 150 ℃ for 20 h. The reaction mixture was concentrated under the reduced pressure and redissolved in CH_2Cl_2 (50 mL). The organic layer was washed with water, followed by brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 0.30 g of dark red materials which was recrystallized from *n*-hexane:CH_2Cl_2 (2:1) to give 0.22 g (89%) of dark brown needles: mp 248-249 ℃. IR (KBr) υ 1606, 1520, 1390, 1340, 1290, 1180, 1112, 982, 930 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 8.56 (s, 1H, H9), 8.14 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.73 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H6), 7.54 (d, *J* = 9.2 Hz, 1H), 7.47 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H7), 7.18 (d, *J* = 13.3 Hz, 1H, =C H-), 5.17 (d, *J* = 13.3 Hz, 1H, =C H-), 2.98 (s, 6H). High resolution MS: 293.21. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 70.15; H, 5.21; N, 14.22.

4-Nitroacridine-3-carbaldehyde (**4**)

A mixture of **3** (0.20 g, 0.68 mmol) and $NaIO_4$ (0.43 g, 0.002 mol) in 15 mL of THF:H_2O (1:1) was stirred for 20 h. Evaporation of the solvent under reduced pressure afforded a dark brown solid which was chromatographed on silica gel eluting with *n*-hexane/CH_2Cl_2 (1:1). The early fractions provide 0.14 g (84%) of yellow needles after recrystallization from *n*-hexane:CH_2Cl_2 (1:1): mp 210-211 ℃. IR (KBr) υ 1710, 1545, 1510, 1396, 1310, 1185, 1063 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 10.31 (s, CHO), 8.92 (s, H9), 8.30 (d, *J* = 9.4 Hz, H1), 8.26 (d, *J* = 9.3 Hz, H5), 8.08 (d, *J* = 8.5 Hz, H8), 8.02 (d, *J* = 8.8 Hz, H2), 7.91 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H6), 7.70 (ddd, *J* = 8.5, 2.4, 1.2 Hz, H7). High resolution MS: 252.12. Anal. Calcd for $C_{14}H_8N_2O_3$: C, 66.67; H, 3.20; N, 11.11. Found: C, 66.71; H, 3.19; N, 11.08.

4-Aminoacridine-3-carbaldehyde (**5**)

Into a solution of **4** (0.10 g, 0.4 mmol) in 5 mL of a mixture of EtOAc:EtOH:H_2O (2:2:1) was

added 0.17 g (0.3 mmol) of iron powder, followed by 1 drop (~1 mL) of conc. HCl. The resulting mixture was refluxed for 1 h, and then filtered. The filtrate was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded yellow solid which was recrystallized from cyclohexane to give 0.054 g (60%) of reddish yellow platelets: mp 159-160 °C. IR (KBr) υ 3455, 3324, 2970, 1650, 1600, 1540, 1494, 1190 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 9.99 (s, 1H, CHO), 8.53 (s, H9), 8.18 (d, *J* = 8.5 Hz, H5), 7.94 (d, *J* = 8.5 Hz, H8), 7.74 (ddd, *J* = 8.5, 7.8, 1.2 Hz, H6), 7.57 (ddd, *J* = 8.5, 7.8, 1.2 Hz, H7), 7.42 (d, *J* = 8.9 Hz, H1), 7.10 (d, *J* = 8.9 Hz, H2). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 192.78, 149.61, 146.88, 140.35, 134.94, 129.87, 129.73, 128.60, 128.35, 128.29, 127.81, 127.24, 113.24, 111.33. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.68; H, 4.54; N, 12.58.

2-(2'-Pyridyl)pyrido[3,2-*c*]acridine (**7a**)

A mixture of **5** (54 mg, 0.24 mmol) and 2-acetylpyridine (**6a**, 30 mg, 0.25 mmol) in 10 mL of dry EtOH with saturated ethanolic KOH (1.3 mL) was refluxed for 12 h. The solvent of the reaction mixture was evaporated under reduced pressure. The resulting pale yellow solid was chromatographed on Al_2O_3, eluting with CH_2Cl_2, followed by CH_2Cl_2:EtOAc (1:1) and EtOAc. The latter fractions of EtOAc afforded 64 mg (86%) of pale yellow crystalline solid which was recrystallized from $CHCl_3$ to give white needles: mp 271 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.28 (d, *J* = 8.0 Hz, H11), 8.91 (d, *J* = 8.3 Hz, H4), 8.89 (ddd, *J* = 4.8, 2.4, 1.2 Hz, H6'), 8.88 (s, H7), 8.71 (d, *J* = 8.8 Hz, H8), 8.35 (d, *J* = 8.4 Hz, H3), 8.07 (d, *J* = 8.1 Hz, 1H, H3'), 7.98 (td, *J* = 7.8, 1.7 Hz, H9/H10), 7.89 (td, *J* = 7.8, 1.7 Hz, H10/H9), 7.88 (d, *J* = 9.0 Hz, H5/6), 7.75 (d, *J* = 9.0 Hz, H6/5), 7.65 (ddd, *J* = 8.4, 7.8, 1.2 Hz, H4'), 7.38 (ddd, *J* = 7.8, 4.8, 1.2 Hz, H5'). ^{13}C NMR (CD_3OD, 62.5 MHz) δ 157.29, 156.91, 150.12, 149.05, 147.93, 146.98, 138.81, 138.48, 138.25, 132.08, 131.12, 130.05, 129.39, 129.08, 128.69, 128.60, 128.18, 127.12, 125.69, 124.30, 122.76. High resolution MS: 307.11. Anal. Calcd for $C_{21}H_{13}N_3 \cdot H_2O$: C, 77.52; H, 4.65; N, 12.92. Found: C, 77.48; H, 4.67; N, 12.89.

2-Phenylpyrido[3,2-*c*]acridine (**7b**)

White needles from EtOH (86%): mp 218-219 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.75 (s, H7),

8.68 (d, *J* = 8.6 Hz, H11), 8.41 (d, *J* = 8.3, 1.5 Hz, 2H, H2' and H6'), 8.23 (d, *J* = 8.3 Hz, H4), 8.10 (d, *J* = 8.3 Hz, H3), 8.04 (d, *J* = 8.3 Hz, H10), 7.86 (ddd, *J* = 8.3, 7.0, 1.5 Hz, H10), 7.82 (d, *J* = 8.3 Hz, H5/6), 7.67 (d, *J* = 8.3 Hz, H6/5), 7.63 (t, *J* = 8.0 Hz, H9), 7.55 (t, *J* = 8.0 Hz, 2H, H3' and H5'), 7.46 (td, *J* = 8.3, 1.5 Hz, H4'). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.36, 148.21, 146.98, 146.52, 139.58, 137.00, 136.48, 131.00, 130.45, 129.61, 128.98, 128.46, 128.14, 127.85, 127.58, 127.27, 127.08, 126.89, 126.08, 121.18. High resolution MS: 306.12. Anal. Calcd for $C_{22}H_{14}N_2$: C, 86.25; H, 4.61; N, 9.14. Found: C, 86.27; H, 4.56; N, 9.17.

2-(2'-Quinolyl)pyrido[3,2-*c*]acridine (**7c**)

White needles from EtOH (92%): mp 271-272 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (d, *J* = 8.0 Hz, H3), 9.06 (d, *J* = 8.0 Hz, H3'), 8.87 (s, H7), 8.85 (d, *J* = 8.0 Hz, H11), 8.37 (d, *J* = 8.0 Hz, H4), 8.33 (d, *J* = 8.4 Hz, H4'), 8.21 (d, *J* = 8.4 Hz, H8'), 8.03 (d, *J* = 8.5 Hz, H8), 7.87 (AB quartet, *J* = 9.0 H, H5/H6), 7.85 (m, H10), 7.83 (d, *J* = 8.0 Hz, H5'), 7.22 (AB quartet, *J* = 9.0 H, H6/H5), 7.70 (t, *J* = 8.5 Hz, H7'), 7.62 (t, *J* = 8.5 Hz, H9), 7.52 (t, *J* = 8.5 Hz, H6'). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 158.87, 155.92, 155.68, 147.70, 147.13, 145.89, 145.07, 138.05, 137.50, 137.27, 131.46, 130.33, 129.94, 129.78, 128.91, 128.06, 128.00, 127.62, 127.53, 127.45, 127.28, 127.12, 126.55, 122.81, 121.01. High resolution MS: 407.14. Anal. Calcd for $C_{25}H_{15}N_3 \bullet 1/2H_2O$: C, 81.95; H, 4.40; N, 11.47. Found: C, 81.92; H, 4.41; N, 11.50.

2-(2'-Naphthyl)pyrido[3,2-*c*]acridine (**7d**)

White needles from EtOH (82%): mp 232-233 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (s, H7), 8.79 (dd, *J* = 8.8, 0.5 Hz, H11), 8.77 (s, H1'), 8.54 (d, *J* = 8.5 Hz, H4), 8.24 (AB quartet, *J* = 9.0 H, 2H, H5 and H6), 8.04-8.01 (m, 2H, H8 and H3'), 7.96 (d, *J* = 8.4 Hz, H3), 7.87 (ddd, *J* = 8.5, 8.0, 1.6 Hz, H9), 7.85 (d, *J* = 8.0 Hz, H5'/H8'), 7.83 (d, *J* = 8.0 Hz, H8'/H5'), 7.69 (d, *J* = 8.8 Hz, H4'), 7.62 (t, *J* = 8.0 Hz, H6'/H7'), 7.51-7.48 (m, 2H, H9 & H7'/H6'). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 157.00, 147.65, 146.43, 146.05, 137.09 (two C's), 136.52, 134.14, 133.67, 130.80, 130.52, 129.26 (two C's), 128.59 (two C's), 127.90, 127.85, 127.68, 127.55, 127.21, 127.17, 126.88, 126.82, 126.40, 126.22, 125.51. High resolution MS: 356.13. Anal. Calcd for $C_{26}H_{16}N_2$: C, 87.62; H, 4.52; N, 7.86. Found: C, 87.60; H, 4.55; N, 7.85.

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