A SYNTHESIS OF 7-SUBSTITUTED 1*H*-PYRANO[4,3-*b*]QUINOLINE DERIVATIVES

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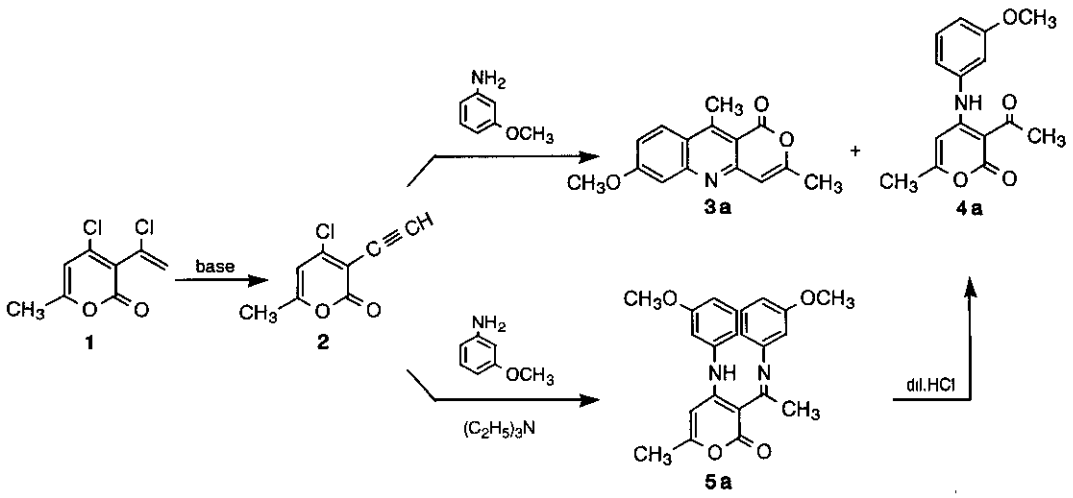
Abstract- The reaction of 4-chloro-3-ethynyl-6-methyl-2*H*-pyran-2-one (**2**) with aniline derivatives having a electron-donating group at the 3-position in EtOH gives 7-substituted 1*H*-pyrano[4,3-*b*]quinolin-1-one derivatives (**3**).

It has been reported that 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (**1**) reacts with appropriate nucleophiles to give various heterocyclic compounds containing pyrone ring such as aminopyrone,[1] pyranopyrazole,[2] pyranobenzodiazepine,[3] and pyranoquinoline.[3]

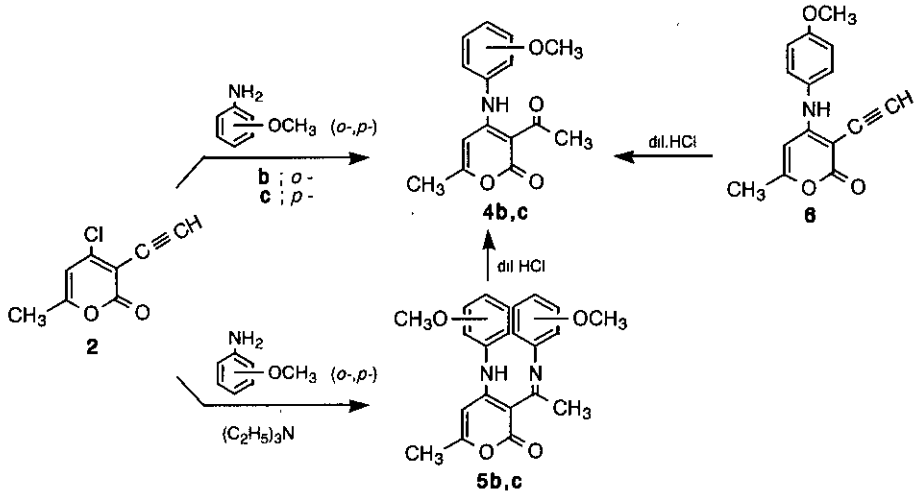
In the preceding paper,[3] we have shown that 4-chloro-3-ethynyl-6-methyl-2*H*-pyran-2-one (**2**) formed by the reaction of **1** with a base is an active intermediate in these reactions, and that only the reaction of **1** and **2** with *m*-phenylenediamine gave a 1*H*-pyrano[4,3-*b*]quinoline (**3**) but such ring formation was not noticed with *o*- and *p*-analogs. These results apparently indicate that the electron-donating character of the 3-amino substituent is essential for the formation of the pyranoquinoline ring system. In order to explore this aspect we examined the reaction of **2** with various substituted anilines.

A mixture of **2** and 2.1 molar eq. amount of *m*-anisidine in EtOH was heated under reflux for 4 h to give the pyranoquinoline (**3a**) in 80 % and the acetylpyrone (**4a**) in 5 % yield. However, on addition of Et_3N as a scavenger of hydrogen chloride in this reaction, the yield of **3a** markedly decrease (2.7 %) and Schiff base of **4a** (**5a**) was formed as the main product. Treatment of the Schiff base (**5a**) with dil. HCl gave the acetylpyrone (**4a**) in 85 % yield. ^{1}H-Nmr spectra of the pyranoquinoline (**3a**) showed three typical signals of a *meta*-coupled proton at 7.25 ppm, an *ortho*- and *meta*-coupled proton at 7.16 ppm, and an *ortho*-coupled proton at 8.06 ppm. Furthermore, the

irradiation of methyl proton at 3.16 ppm of **3a** gives NOE (3%) on an *ortho*-coupled proton at 8.06 ppm. These data are well consistent with the structure of **3a** as 7-methoxy-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one.

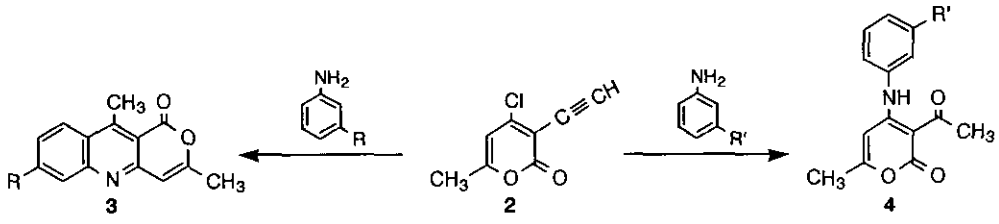


Scheme 1



Scheme 2

On the other hand, the reaction of **2** with 2.1 molar eq. amount of *o*- or *p*-anisidine, respectively, in the absence of Et_3N gave acetylpyrones (**4b,c**); the corresponding pyranoquinolines were not obtained. These reactions in the presence of Et_3N gave Schiff bases (**5b,c**), which gave acetylpyrones (**4b,c**) upon treatment with dil. HCl. The acetylpyrone (**4c**) was also obtained by hydrolyzing the 3-ethynylpyrone (**6**) which was prepared from the reaction of **2** with *p*-anisidine at room temperature. Treatment of **2** with anilines having an electron-donating group, such as NMe_2, NH_2, and OH, at the 3-position under the first mentioned conditions afforded pyranoquinolines (**3b-d**) in good yields. However, reactions of **2** with 3-ethylaniline, 3-halogenoanilines, and aniline gave only the corresponding acetylpyrones (**4d-i**). The structures of all products were determined by the spectral and analytical evidence.

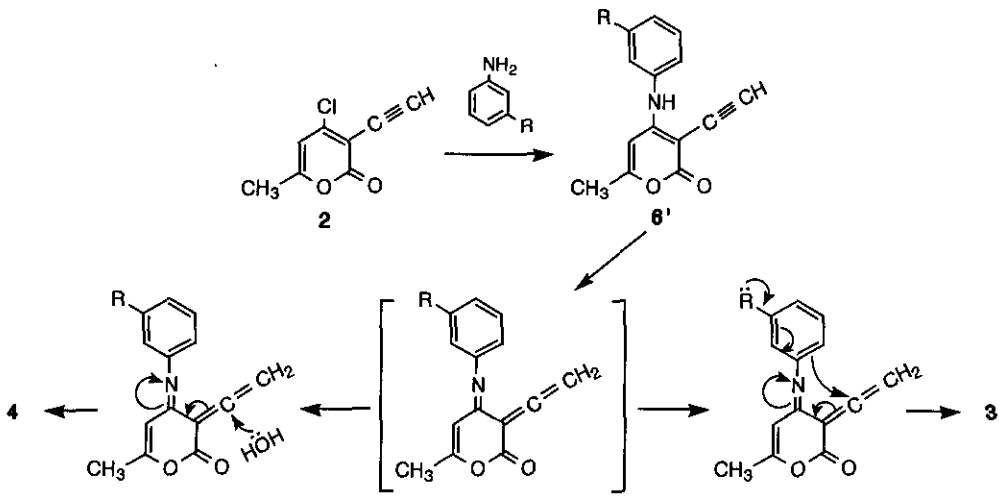


b : R = $N(CH_3)_2$
c : R = NH_2
d : R = OH

d : R' = C_2H_5
e : R' = F
f : R' = Cl
g : R' = Br
h : R' = I
i : R' = H

Scheme 3

A probable route of the ring formation of pyranoquinoline by the reaction of **2** with aniline derivatives may be postulated as shown in Scheme 4. Thus, **2** reacts with anilines to give first 4-anilino-3-ethynylpyrone (**6'**); **6** was successfully isolated from the reaction of **2** with *p*-anisidine at room temperature. If a substituent at the 3-position of aniline has strong electron-donating effect, the ring formation occurs at the 6-position of the aniline to give pyranoquinoline (**3**). However, if it has little or no such effect, **6'** was hydrolyzed to give acetylpyrones (**4**). Under basic conditions, **6'** preferentially reacts with excess anilines to give Schiff bases (**5**).



Scheme 4

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were taken with Hitachi Model 260-10 spectrophotometer. Ms spectra were measured on JEOL JMS-DX303/LMA-DA5000 instrument. ^{1}H-Nmr spectra were recorded on JEOL JNM-GSX400 and JNM-PMX60SI spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard.

Reaction of 2 with anilines ; General procedure : A mixture of **2** (1 g, 5.9 mmol) and anilines (12 mmol) in EtOH (70 ml) was heated under reflux for 4 h. The precipitate was collected by filtration, washed with water, and then recrystallized. The filtrate was concentrated, and the residue was diluted with $CHCl_3$ (60 ml). The solution was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$.

7-Methoxy-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3a) : Yield of 80 %, mp 196-197 ℃ (EtOH), ir (KBr) : 1725, 1680, 1620 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.31 (s, 3H, 3-CH_3), 3.16 (s, 3H, 10-CH_3), 3.97 (s, 3H, OCH_3), 6.42 (s, 1H, 4-H), 7.16 (dd, 1H, 8-H, J = 9.0 and 2.5 Hz), 7.25 (d, 1H, 6-H, J = 2.5 Hz), 8.06 (d, 1H, 9-H, J = 9.0 Hz), ms (*m/z*) : 255 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.59 ; H, 5.10 ; N, 5.49. Found : C, 70.75 ; H, 5.07 ; N, 5.50.

3,10-Dimethyl-7-dimethylamino-1*H*-pyrano[4,3-*b*]quinolin-1-one (3b) : Yield of 78 %, mp 228-229 ℃ (EtOH), ir (KBr) : 1725, 1680, 1620 cm^{-1}, ^{1}H-nmr ($CDCl_3$-CF_3COOD) δ 2.43 (s, 3H, 3-CH_3), 3.23 (s, 3H, 10-CH_3), 3.30 (s, 6H, $N(CH_3)_2$), 6.70 (s, 1H, 4-H), 6.89 (d, 1H, 6-H, J = 2.4 Hz), 7.30 (dd, 1H, 8-H, J = 9.0 and 2.4 Hz), 8.21 (d, 1H, 9-H, J = 9.0 Hz), ms (*m/z*) : 268 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64 ; H, 5.97 ; N, 10.45. Found : C, 71.75 ; H, 6.13 ; N, 10.25.

7-Amino-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3c) : Yield of 82 %, mp 299 ℃ (decomp., EtOH), ir (KBr) : 1715, 1670, 1635 cm^{-1}, ^{1}H-nmr (DMSO-d_6) δ 2.49 (s, 3H, 3-CH_3), 3.27 (s, 3H, 10-CH_3), 6.33 (br s, 2H, NH_2), 6.40 (s, 1H, 4-H), 6.91 (d, 1H, 6-H, J = 2.0 Hz), 7.02 (dd, 1H, 8-H, J = 9.0 and 2.0 Hz), 8.03 (d, 1H, 9-H, J = 9.0 Hz), ms (*m/z*) : 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00 ; H, 5.00 ; N, 11.67. Found : C, 69.96 ; H, 4.95 ; N, 11.58.

7-Hydroxy-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one (3d) : Yield of 72 %, mp 288-289 ℃ (decomp., EtOH), ir (KBr) : 1740, 1670, 1620 cm^{-1}, ^{1}H-nmr ($CDCl_3$-CF_3COOD) δ 2.48 (s, 3H, 3-CH_3), 3.39 (s, 3H, 10-CH_3), 6.75 (s, 1H, 4-H), 7.44 (dd, 1H, 8-H, J = 9.0 and 2.4 Hz), 7.72 (d, 1H, 6-H, J = 2.4 Hz), 8.36 (d, 1H, 9-H, J = 9.0 Hz), ms (*m/z*) : 241 (M^+). *Anal.* Calcd for $C_{14}H_{11}NO_3$: C, 69.71 ; H, 4.56 ; N, 5.81. Found : C, 69.45 ; H, 4.59 ; N, 5.67.

3-Acetyl-4-(3-methoxyanilino)-6-methyl-2*H*-pyran-2-one (4a) : Yield of 5 %, mp 170-171 ℃ (MeOH or Et_2O), ir (KBr) : 1710, 1655, 1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 5.94 (s, 1H, 5-H), 6.73-7.57 (m, 4H, Ar-H), 13.02 (br s, 1H, NH), ms (*m/z*) : 273 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93 ; H, 5.49 ; N, 5.13. Found : C, 65.69 ; H, 5.50 ; N, 5.13.

3-Acetyl-4-(2-methoxyanilino)-6-methyl-2*H*-pyran-2-one (4b) : Yield of 72.5 %, mp 147-148 ℃ (Et_2O), ir (KBr) : 1730, 1660, 1595 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.17 (s, 3H, CH_3), 2.71 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 5.84 (s, 1H, 5-H), 6.85-7.50 (m, 4H, Ar-H), 12.95 (br s, 1H, NH), ms (*m/z*) : 273 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93 ; H, 5.49 ; N, 5.13. Found : C, 65.85 ; H, 5.59 ; N, 5.35.

3-Acetyl-4-(4-methoxyanilino)-6-methyl-2*H*-pyran-2-one (4c) : Yield of 76 %, mp 154-155

℃ (Et_2O), ir (KBr) : 1710, 1660, 1610 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 2.68 (s, 3H, $COCH_3$), 3.87 (s, 3H, OCH_3), 5.81 (s, 1H, 5-H), 6.85-7.35 (m, 4H, Ar-H), 12.87 (br s, 1H, NH), ms (*m/z*) : 273 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93 ; H, 5.49 ; N, 5.13. Found : C, 66.29 ; H, 5.56 ; N, 5.08.

3-Acetyl-4-(3-ethylanilino)-6-methyl-2*H*-pyran-2-one (4d) : Yield of 74.6 %, mp 121-122 ℃ (petroleum ether), ir (KBr) : 1710, 1655, 1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.26 (t, 3H, CH_2-$\underline{CH_3}$, J = 7.6 Hz), 2.14 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 2.71 (q, 2H, $\underline{CH_2}$-CH_3, J = 7.6 Hz), 5.88 (s, 1H, 5-H), 6.89-7.55 (m, 4H, Ar-H), 13.06 (br s, 1H, NH), ms (*m/z*) : 271 (M^+). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.85 ; H, 6.27 ; N, 5.17. Found : C, 71.05 ; H, 6.32 ; N, 4.99.

3-Acetyl-4-(3-fluoroanilino)-6-methyl-2*H*-pyran-2-one (4e) : Yield of 62.6 %, mp 172-173 ℃ (Et_2O), ir (KBr) : 1720, 1655, 1610 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 5.89 (s, 1H, 5-H), 6.80-7.66 (m, 4H, Ar-H), 13.24 (br s, 1H, NH), ms (*m/z*) : 261 (M^+). *Anal.* Calcd for $C_{14}H_{12}NO_3F$: C, 64.37 ; H, 4.60 ; N, 5.36. Found : C, 64.51 ; H, 4.54 ; N, 5.13.

3-Acetyl-4-(3-chloroanilino)-6-methyl-2*H*-pyran-2-one (4f) : Yield of 71 %, mp 203-204 ℃ (Et_2O), ir (KBr) : 1720, 1655, 1610 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.70 (s, 3H, $COCH_3$), 5.87 (s, 1H, 5-H), 6.99-7.50 (m, 4H, Ar-H), 13.23 (br s, 1H, NH), ms (*m/z*) : 277 (M^+). *Anal.* Calcd for $C_{14}H_{12}NO_3Cl$: C, 60.54 ; H, 4.32 ; N, 5.05. Found : C, 60.73 ; H, 4.30 ; N, 4.96.

3-Acetyl-4-(3-bromoanilino)-6-methyl-2*H*-pyran-2-one (4g) : Yield of 66 %, mp 211-212 ℃ (Et_2O), ir (KBr) : 1720, 1655, 1610 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 5.89 (s, 1H, 5-H), 7.07-7.69 (m, 4H, Ar-H), 13.11 (br s, 1H, NH), ms (*m/z*) : 321 (M^+). *Anal.* Calcd for $C_{14}H_{12}NO_3Br$: C, 52.19 ; H, 3.73 ; N, 4.35. Found : C, 52.06 ; H, 3.63 ; N, 4.30.

3-Acetyl-4-(3-iodoanilino)-6-methyl-2*H*-pyran-2-one (4h) : Yield of 55 %, mp 186-187 ℃ (MeOH), ir (KBr) : 1720, 1655, 1610 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.69 (s, 3H, $COCH_3$), 5.87 (s, 1H, 5-H), 7.17-7.88 (m, 4H, Ar-H), 13.06 (br s, 1H, NH), ms (*m/z*) : 369 (M^+). *Anal.* Calcd for $C_{14}H_{12}NO_3I$: C, 45.54 ; H, 3.25 ; N, 3.80. Found : C, 45.83 ; H, 3.24 ; N, 3.78.

3-Acetyl-4-anilino-6-methyl-2*H*-pyran-2-one (4i) : Yield of 64 %, mp 155 ℃ (Et_2O), ir (KBr) : 1715, 1655, 1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 2.70 (s, 3H, $COCH_3$), 5.88 (s, 1H, 5-H), 7.10-7.57 (m, 5H, Ar-H), 13.13 (br s, 1H, NH), ms (*m/z*) : 243 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.14 ; H, 5.35 ; N, 5.76. Found : C, 68.91 ; H, 5.45 ; N, 5.63.

Preparation of Schiff bases (5a-c) ; General procedure : A mixture of **2** (1 g, 5.9 mmol), anilines (12 mmol), and Et_3N (1.2 g, 12 mmol) in EtOH (70 ml) was heated under reflux for 4 h. The reaction mixture was concentrated, and the residue was diluted with $CHCl_3$ (60 ml). The solution was washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$.

***N*-(3-Methoxyphenyl)-1-[4-(3-methoxyanilino)-6-methyl-2-oxo-2*H*-pyran-3-yl]ethylidene-amine (5a)** : Yield of 65 %, mp 128-129 ℃ (Et_2O), ir (KBr) : 1710, 1660, 1605 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 2.46 (s, 3H, N=C-CH_3), 3.84 (s, 6H, $OCH_3 \times 2$), 6.03 (s, 1H, CH=), 6.39-7.53 (m, 8H, Ar-H), 14.34 (br s, 1H, NH), ms (*m/z*) : 378 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.84 ; H, 5.82 ; N, 7.41. Found : C, 69.68 ; H, 6.06 ; N, 7.12.

***N*-(2-Methoxyphenyl)-1-[4-(2-methoxyanilino)-6-methyl-2-oxo-2*H*-pyran-3-yl]ethylidene-amine (5b)** : Yield of 78 %, mp 155-156 ℃ (EtOH), ir (KBr) : 1700, 1660, 1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 2.41 (s, 3H, N=C-CH_3), 3.76 and 3.83 (s, 6H, $OCH_3 \times 2$), 5.91 (s, 1H, CH=), 6.75-7.49 (m, 8H, Ar-H), 14.06 (br s, 1H, NH), ms (*m/z*) : 378 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.84 ; H, 5.82 ; N, 7.41. Found : C, 69.74 ; H, 5.96 ; N, 7.15.

***N*-(4-Methoxyphenyl)-1-[4-(4-methoxyanilino)-6-methyl-2-oxo-2*H*-pyran-3-yl]ethylidene-amine (5c)** : Yield of 57 %, mp 98-99 ℃ (Et_2O - petroleum ether, 1 : 3 v/v), ir (KBr) : 1700, 1660, 1600 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.45 (s, 3H, N=C-CH_3), 3.79 and 3.81 (s, 6H, $OCH_3 \times 2$), 5.90 (s, 1H, CH=), 6.64-7.37 (m, 8H, Ar-H), 14.45 (br s, 1H, NH), ms (*m/z*) : 378 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.84 ; H, 5.82 ; N, 7.41. Found : C, 69.72 ; H, 5.84 ; N, 7.19.

Hydrolysis of Schiff base (5) with dil. HCl ; General procedure : A mixture of **5** (0.5 g, 1.3 mmol) and 10 % aqueous HCl (1 ml) in EtOH (10 ml) was heated at 60 ℃ for 30 min.

The reaction mixture was concentrated, and the residue was diluted with $CHCl_3$ (60 ml). The solution was washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$ to give acetylpyrone (**4**). Yields of **4a**, **4b**, and **4c** were 85 %, 92 %, and 91 %, respectively.

3-Ethynyl-4-(4-methoxyanilino)-6-methyl-2*H*-pyran-2-one (6) : A mixture of **2** (1 g, 5.9 mmol) and *p*-anisidine (0.8 g, 6.5 mmol) in EtOH (70 ml) was stirred for 1 h at 0 ℃. The resulting mixture was warmed to room temperature, and then the solvent was removed *in vacuo* at ambient temperature. The residue was purified by column chromatography on silica gel with $CHCl_3$, and recrystallized from Et_2O to give 0.52 g (34.4 %) of **6** ; mp 139-140 ℃, ir (KBr) : 2100, 1720, 1650 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 3.66 (s, 1H, C≡CH), 3.87 (s, 3H, OCH_3), 5.78 (s, 1H, 5-H), 6.88-7.34 (m, 5H, NH and Ar-H), ms (*m/z*) : 255 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_3$: C,70.59; H, 5.10 ; N, 5.49. Found : C, 70.68 ; H, 5.08 ; N, 5.46. Hydrolysis of **6** by the same procedure described above gave acetylpyrone (**4c**) in 87 % yield.

REFERENCES

1. Y. Azuma, A. Sato, K. Tanno, M. Madarame, and S. Hisamichi, *Annu. Rep. Tohoku Coll. Pharm.* 1988, **35**, 221 [*Chem. Abstr.*, 1990, **112**, 178560b] ; *idem*, *ibid.*, 1989, **36**, 219 [*Chem. Abstr.*, 1991, **114**, 143052b].
2. A. Cantos, P. De March, M. Moreno-Manas, A. Pla, F. Sanchez-Ferrando, and A. Virgili, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4425 ; *idem*, *Chem. Lett.*, **1986**, 295.
3. Y. Azuma, A. Sato, and M. Morone, *Heterocycles*, 1993, **35**, 599.

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