Synthesis of 4-Heterocyclyl-hexahydro-8-methoxyfuro[3,2-*c*]quinolines by Lewis Acid Catalyzed [4 + 2]Cycloaddition Reaction

Tetsuji Kametani*, Hiroko Furuyama, Yukari Fukuoka, Hajime Takeda, Yukio Suzuki, and Toshio Honda

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Received July 2, 1985

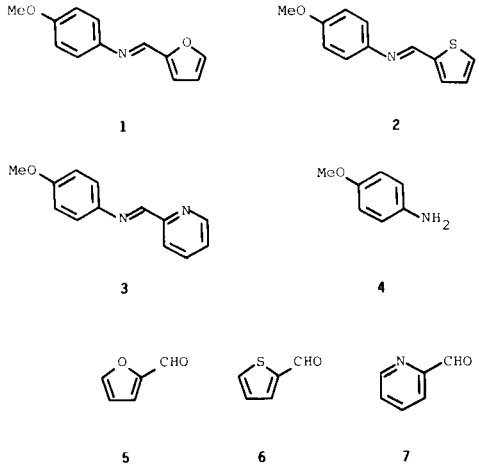
Synthesis of 2-substituted quinoline derivatives by Lewis acid catalyzed [4 + 2]cycloaddition was investigated.

J. Heterocyclic Chem., **23**, 185 (1986).

Multifunctional polycyclic natural products containing a quinoline ring which is substituted by aromatic functional group at 2-position, such as streptonigrin, lavendamycin and so on, indicate an antitumor activity. Moreover, the quinoline skeleton is expected to be a synthon of camptothecin. Therefore, several attempts to synthesize the 2-substituted quinoline derivatives have been tried to date [1]. We have recently reported the synthesis of quinoline ring system by Lewis acid catalyzed [4 + 2]cycloaddition reactions [2]. We now wish to report the [4 + 2]cycloaddition reaction of the Schiff base as a diene with 2,3-dihydrofuran as a dienophile.

Firstly, the Schiff bases **1**, **2**, and **3** were synthesized by the reaction of *p*-anisidine (**4**) with furfural (**5**), 2-thiocarboxaldehyde (**6**), and 2-pyridinecarboxaldehyde (**7**), respectively, in the presence of magnesium sulfate at room temperature.

Scheme 1



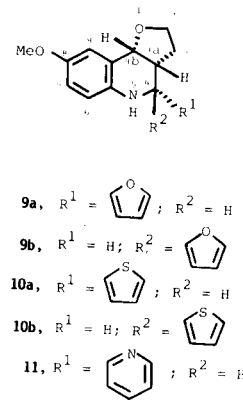
1 2 3 4 5 6 7

Subsequently, the [4 + 2]cycloaddition reaction of the Schiff base **1** with 2,3-dihydrofuran (**8**) in dry methylene chloride in the presence of tin tetrachloride as Lewis acid at room temperature afforded the adducts **9a** and **9b** (formation ratio, 5:1), whose structures including stereochemistry were determined based on their nmr data.

Similarly, the reaction of the Schiff base **2** with **8** in the presence of tin chloride also brought about the cycloaddition to afford the adducts **10a** and **10b** (formation ratio, 1:1). The reaction of the Schiff base **3** with **8** in the presence of tin tetrachloride also brought about the cycloaddition to yield the adduct **11**.

When these reactions were carried out in the presence of boron trifluoride etherate as Lewis acid, none of the desired product was formed.

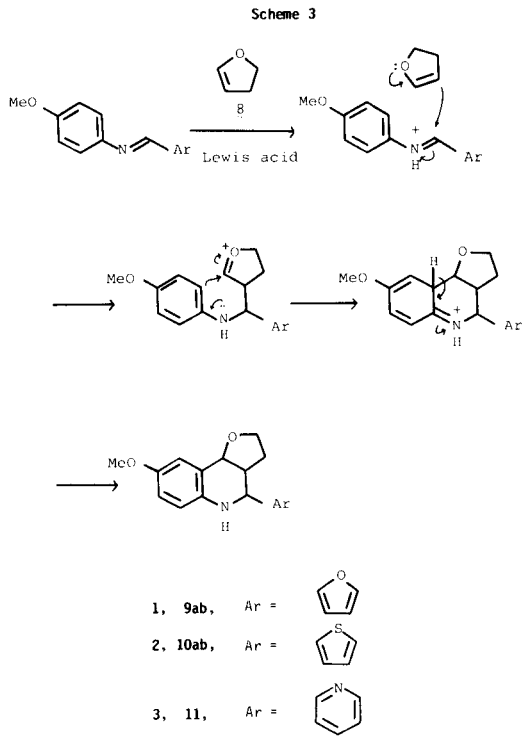
Scheme 2



Regarding the reaction mechanism as shown in Scheme 3, the products were obtained.

The stereochemistry at 3a-, 4-, and 9b-positions was determined according to Elslager and Worth [3]. In the nmr spectrum of **9a**, the proton of 9b-position was assigned at 5.2 ppm as doublet (J = 8 Hz), which showed that the configuration between 3a- and 9b-position should be *cis*. Furthermore, the proton of 4-position was also assigned at 4.6 ppm as doublet (J = 2 Hz), which showed the configuration between 3a- and 4-position should be *cis*. On the other hand, in case of **9b**, the proton of 9b-position was assigned at 4.6 ppm as doublet (J = 6 Hz), by the result of which the configuration between 3a- and 9b-position should be *cis*. In this case the signal of the proton of 4-position could not be found because of the presence of methoxy group

Scheme 3



and so on. Thus configuration between 3a-and 4-position should be *trans*.

Although the stereochemistry had been determined as above, the formation of regioisomer **9c** could not be ruled out. Though, the proton of 9b-position should be shown as multiplet in case of **9c**, it is actually observed as doublet. Therefore, the formation of **9c** was denied.

[4 + 2]Cycloaddition reaction of the Schiff base possessing pyridine ring with various dienophiles is under investigation.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured on a Hitachi 260-10 spectrophotometer, nmr spectra with a JEOL JNM-PMX 60 spectrometer using tetramethylsilane as an internal standard with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were taken with a JEOL JMS-D 300 spectrometer.

4-(α-Furyl)-2,3,3aβ,4β,5,9bβ-hexahydro-8-methoxyfuro[3,2-*c*]quinoline (**9a**) and 4-(α-Furyl)-2,3,3aβ,4α,5,9bβ-hexahydro-8-methoxyfuro[3,2-*c*]-quinoline (**9b**).

To a stirred solution of *p*-anisidine (**4**) (11.26 g) (0.09 mole) and furfural (8.76 g) (0.09 mole) in benzene (200 ml) was added magnesium sulfate (10.0 g). After stirring for 20 hours at room temperature, the reaction mixture was filtered. The organic layer separated was evaporated to give a yellowish solid. Crystallization from dichloromethane-*n*-hexane afforded the Schiff base **1** as colorless needles, mp 68.5-69.0°; ir (chloroform): 1620 cm^{-1} (C=N), 1580 cm^{-1} (C=C); nmr (deuteriochloroform): δ 3.7 (s, 3H, CH_3O-), 6.4-7.6 (m, 7H, 4 × ArH and 3 × heterocyclic H), 8.2 (s, 1H, -N=C*H*-); ms: m/e 201 (M^+).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.70; H, 5.41; N, 6.95.

To a stirred solution of **1** (2.0 g) (10.6 mmoles) in dry dichloromethane (20 ml) was added 30 drops of stannic chloride. After stirring for 10 minutes, 2,3-dihydrofuran (**8**) (1.48 g) (21.2 mmoles) in dry dichloromethane (5 ml) was added dropwise within 25.5 hours at room temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution cooled with ice. After stirring for 30 minutes, the solution was extracted with dichloromethane. The organic layer separated was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give a residue, to which 2% hydrochloric acid soluiton (20 ml) was added and then the aqueous layer was washed with ether. The above aqueous layer was basified with ammonia and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated to give a brown oil, which was purified by silica gel column chromatography.

The elution with benzene-ethyl acetate (95:5 v/v) afforded **9a** (300 mg, 13.0%) as colorless needles, mp 141.5-142.0° (dichloromethane-*n*-hexane); ir (chloroform): 3390 cm^{-1} (NH); nmr (deuteriochloroform): δ 1.4-2.4 (m, 2H, -OCH$_2$C*H*$_2$-), 2.8-3.1 (m, 1H, -OCH$_2$CH$_2$C*H*<), 3.5-4.0 (m, 6H, C*H*$_3$O- and -OC*H*$_2$- and N*H*), 4.6 (d, 1H, $J_{3a,4}$ = 2 Hz *(cis)*, -NHC*H*<), 5.2 (d, 1H, $J_{3a,9b}$ = 8 Hz *(cis)*, -OC*H*<), 6.2-7.4 (m, 6H, 3 × ArH and 3 × heterocyclic H); ms: m/e 271 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.92; H, 6.36; N, 5.06.

The second elution afforded **9b** (60 mg, 4.5%) as colorless needles, mp 101.5-102.0° (dichloromethane-*n*-hexane); ir (chloroform): 3380 cm^{-1} (NH); nmr (deuteriochloroform): δ 1.4-2.3 (m, 2H, -OCH$_2$C*H*$_2$-), 2.3-2.8 (m, 1H, -OCH$_2$CH$_2$C*H*<), 3.5-4.1 (m, 7H, C*H*$_3$O- and -OC*H*$_2$- and N*H* and -NHC*H*<), 4.6 (d, 1H, $J_{3a,9b}$ = 6 Hz *(cis)*, -OC*H*<), 6.2-7.4 (m, 6H, 3 × ArH and 3 × heterocyclic H); ms: m/e 271 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.91; H, 6.36; N, 5.02.

4-(α-Thienyl)-2,3,3aβ,4β,5,9bβ-hexahydro-8-methoxyfuro[3,2-*c*]quinoline (**10a**) and 4-(α-Thienyl)-2,3,3aβ,4α,5,9bβ-hexahydro-8-methoxyfuro-[3,2-*c*]quinoline (**10b**).

To a stirred solution of *p*-anisidine (**4**) (14.47 g) (0.12 mole) and 2-thiophenecarboxaldehyde (**6**) (13.18 g) (0.12 mmoles) in benzene (200 ml) was added magnesium sulfate (14.0 g). After stirring for 20 hours at room temperature, the reaction mixture was treated as in case of **1** to give the Schiff base **2** (25.2 g, 99%) as colorless needles, mp 47.5-48.0°; ir (chloroform): 1630 cm^{-1} (C=N), 1590 cm^{-1} (C=C); nmr (deuteriochloroform): δ 3.8 (s, 3H, C*H*$_3$O-), 6.5-7.6 (m, 7H, 4 × ArH and 3 × heterocyclic H), 8.4 (s, 1H, -N=C*H*-); ms: m/e 217 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.69; H, 5.04; N, 6.48.

To a stirred solution of **2** (2.0 g) (9.76 mmoles) in dry dichloromethane (20 ml) was added 30 drops of stannic chloride. After stirring for 10 minutes a solution of 2,3-dihydrofuran (**8**) (1.79 g) (25.7 mmoles) in dry dichloromethane (5 ml) was added dropwise within 42.5 hours at room temperature. The reaction mixture was treated as in case of **9**. The residue was purified by silica gel column chromatography. The elution with benzene-ethyl acetate (95:5 v/v) afforded **10a** (233 mg, 8.3%) as colorless needles, mp 147.5-148.0° (dichloromethane-*n*-hexane); ir (chloroform): 3390 cm^{-1} (NH); nmr (deuteriochloroform): δ 1.1-3.0 (m, 3H, -OCH$_2$C*H*$_2$- and -OCH$_2$CH$_2$C*H*<), 3.5-4.0 (m, 6H, C*H*$_3$O- and -OC*H*$_2$- and N*H*), 4.9 (d, 1H, $J_{3a,4}$ = 2 Hz *(cis)*, -NHC*H*<), 5.2 (d, 1H, $J_{3a,9b}$ = 8 Hz *(cis)*, -OC*H*<), 6.4-7.5 (m, 6H, 3 × ArH and 3 × heterocyclic H); ms: m/e 278 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.97 N, 4.87. Found: C, 66.93; H, 5.91; N, 4.79.

The second elution afforded **10b** (266 mg, 8.1%) as colorless needles, mp 109.5-110.0° (dichloromethane-*n*-hexane); ir (chloroform): 3400 cm^{-1} (NH); nmr (deuteriochloroform): δ 1.7-2.7 (m, 3H, -OCH$_2$C*H*$_2$- and -OCH$_2$CH$_2$C*H*<), 3.7-4.3 (m, 7H, C*H*$_3$O- and -OC*H*$_2$- and N*H* and -NHC*H*<), 4.6 (d, 1H, $J_{3a,9b}$ = 6 Hz *(cis)*, -OC*H*<), 6.5-7.7 (m, 6H, 3 × ArH and 3 × heterocyclic H); ms: m/e 287 (M^+).

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 67.33; H, 5.99; N, 4.93.

4-(α-Pyridyl)-2,3,3aβ,4β,5,9bβ-hexahydro-8-methoxyfuro[3,2-*c*]quinoline (**11**).

To a stirred solution of *p*-anisidine (**4**) (12.32 g) (0.10 mole) and 2-pyridinecarboxaldehyde (**7**) (10.71 g) (0.10 mole) in benzene (200 ml) was added 12.0 g of magnesium sulfate. The reaction mixture was treated as in case of **1** to give the Schiff base **3** (20.8 g, 98%) as a brown oil; ir (chloroform): 1620 cm^{-1} (C=N), 1580 cm^{-1} (C=C); nmr (deuteriochloroform): δ 3.8 (s, 3H, CH_3O-), 6.5-8.3 (m, 7H, 4 × ArH and 3 × heterocyclic H), 8.6 (m, 2H, 2 × -N=C*H*-); ms: m/e 212 (M^+); high resolution ms: Calcd. $C_{13}H_{12}N_2O$: m/e 212.2514 (M^+). Found: m/e 212.0926 (M^+).

To a stirred solution of **3** (2.0 g) (9.39 mmoles) in dry dichloromethane (20 ml) was added 20 drops of stannic chloride. After stirring for 10 minutes, a solution of 2,3-dihydrofuran (**8**) (1.31 g) (28.17 mmoles) in dry dichloromethane (5 ml) was added dropwise within 48 hours at room temperature. Additional 10 drops of stannic chloride was added and stirred for 25 hours. Furthermore, 10 drops of stannic chloride was added and stirred for 24 hours. The reaction mixture was treated as in case of **9**, and the residue was purified by silica gel column chromatography.

The elution with benzene-ethyl acetate (70:30 v/v) afforded **11** (442 mg, 17%) as colorless needles, mp 136.5-137.0° (dichloromethane-*n*-hexane); ir (chloroform): 3380 cm^{-1} (NH); nmr (deuteriochloroform): δ 2.6-3.2 (m, 3H, -OCH_2CH_2- and -OCH_2CH_2CH<), 3.5-4.4 (m, 6H, CH_3O- and -OCH_2- and N*H*), 4.7 (d, 1H, $J_{3a,4}$ = 2 Hz *(cis)*, -NHC*H*<), 5.3 (d, 1H, $J_{3a,9b}$ = 8 Hz *(cis)*, -OC*H*<), 6.4-8.9 (m, 7H, ArH); ms: m/e 282 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.35; H, 6.41; N, 9.85.

Acknowledgements.

We thank Mrs. T. Ogata, Miss T. Tanaka, and Miss M. Moriki of Hoshi University for microanalyses, spectral measurements, and Manuscript preparation.

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