PRACTICAL SYNTHESIS OF QUINOLINE NUCLEUS OF NK-104

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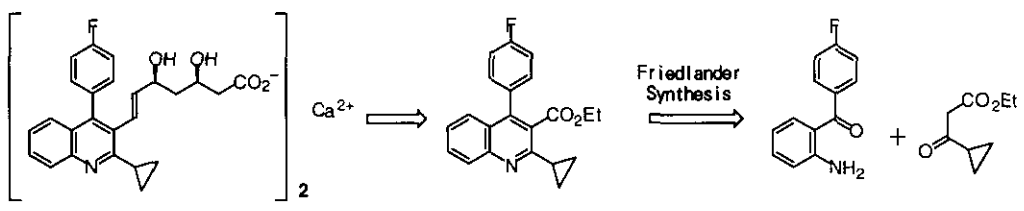
Abstract — The development of practical synthetic procedure for a staple intermediate of NK-104, a highly advanced HMG-Co.A reductase inhibitor is reported.

In our search for a highly advanced inhibitor of HMG-Co. A (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, the rate-limiting enzyme in sterol biosynthesis in animals and plants,[1] NK-104(monocalcium bis[(3*R*, 5*S*, 6*E*)-7-(2-cyclopropyl-4-(4'-fluorophenyl)-3-quinolyl)-3,5-dihydroxy-6-heptenoate], **1**) was found. NK-104 was becoming prominent for reducing both serum cholesterol and triglyceride with significant effectiveness and high potency in clinical evaluations.[2] Up to this time, several efficient syntheses of NK-104 had been achieved by our group and collaborators.[3] In these routes, ethyl 2-cyclopropyl-4-(4'-fluorophenyl)quinoline-3-carboxylate (**2**) is a first staple intermediate to elaborate the optical active desmethyl mevalonic acid chain on the quinoline nucleus. We adopted Friedlander quinoline synthesis shown in Scheme 1 to obtain **2**. In this paper we report on a practical synthetic procedure for the industrial production of target (**2**) focusing on the optimized condition of Friedlander reaction.

Scheme 1



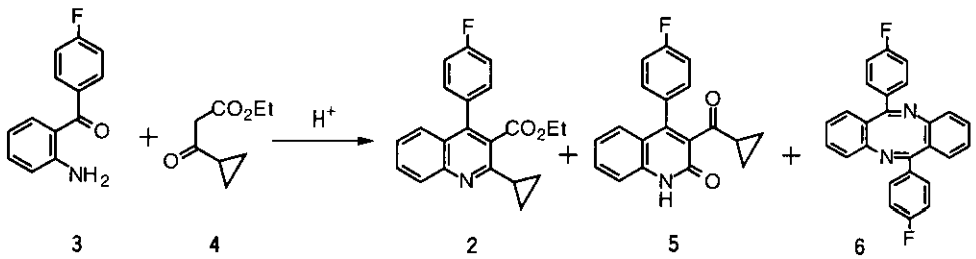
1:NK-104 2 3 4

Several 2-alkyl-4-arylquinoline-3-carboxylates were prepared by acid catalyzed Friedlander syntheses from *o*-aminobenzophenones and simple aliphatic β-keto esters. Fehnel developed a useful procedure in which the condensation was carried out in refluxing acetic acid with a small amount of sulfuric acid.[4] We tried dehydration-condensation reaction of 2-amino-4'-fluorobenzophenone (**3**) with ethyl 3-cyclopropyl-3-oxopropanoate (**4**) by the Fehnel modification. The yield of desired **2** remained 73.9 % at most, and the method has drawback in isolation of the product. Another procedure in which the condensation is carried out in toluene under reflux in the presence of a small amount of *p*-toluenesulfonic acid also provides 2-alkyl-4-arylquinoline-3-carboxylates.[5] We surmised that the latter method was more convenient for

industrial production, because aromatic hydrocarbon solvents would provide simple work-up procedure. Although we needed purification by chromatography, our early small scale experiments using **3** and **4** showed that *p*-toluenesulfonic acid catalyzed Friedlander synthesis in refluxing toluene yielded the target (**2**) in a nearly 90 % yield, and moreover the reaction rate was fast (run 4 in Table 1).[6] Therefore, we supposed this procedure to be worth trying further investigation to optimize the reaction.

In this case, we obtained 3-cyclopropanecarbonyl-4-(4'-fluorophenyl)-2-quinolone (**5**) as by-product in a considerable yield. This undesirable acylcarbostyril (**5**) is a common condensation product of aminobenzophenon (**3**) with ester-carbonyl group in **4** under neutral condition.[7] Since **5** is a high polar and crystalline material, its elimination by recrystallization injured the yield of **2** greatly. Another problem in this method was a self-condensation of **3** under acidic conditions. Various acid catalyzed Friedlander syntheses of **2** gave the dimer from **3**, 6,12-bis(4'-fluorophenyl)dibenzo[*b*,*f*]-[1,5]diazocine (**6**) significantly.[8] The dimer (**6**) has a very similar property compared to **2**, and reduced the yield of target (**2**). The absence of efficient synthetic method of **2** let us investigate to find an optimized reaction condition which would suppress the production of these undesirable side products, and could provide the target (**2**) selectively.

Scheme 2



3 **4** **2** **5** **6**

Our examination using *p*-toluenesulfonic acid in an amount of up to 0.2 equivalent to **3** in refluxing toluene gave the following information(Table 1). Namely, the reaction without acid catalyst did not give **2** at all, and the only product was **5** under neutral condition. The amount of *p*-toluenesulfonic acid used affected the selectivity ratio of **2**/(**2**+**5**) markedly. The amount of dimer (**6**) was also reduced considerably by sufficient addition of the acid catalist. Further experiments were made to clarify the optimized condition, using these data as a basis.

Table 1 PTS catalyzed Friedlander syntheses of **2** in refluxing toluene.

run	PTS (equiv. to **3**)	time (hr)	mol%[a] **3**	**6**	**2**	**5**	mol fraction **2**/(**2**+**5**)
1	none	3	74.8	0	0	25.2	0
2	0.05	10	0.7	5.1	66.6	27.6	0.71
3	0.1	5	0.8	4.0	80.6	14.6	0.85
4	0.2	5	0.4	3.2	86.9	9.6	0.90

a) Estimated from area ratio of the products by HPLC.

Table 2 Acid catalyzed Friedlander syntheses of **2** in refluxing benzene.

run	acid (equiv. to **3**)	time (hr)	mol%[a] **3**	**6**	**2**	**5**	mol fraction **2**/(**2**+**5**)
1	PTS (0.2)	4	0.5	4.4	90.7	4.4	0.95
2	MSA (0.2)	4	2.3	2.0	92.9	2.9	0.97
3	(1)	4	2.4	trace	96.2	1.4	0.99
4	CCl_3CO_2H (0.2)	4	20.8	0.9	75.3	3.0	0.96
5	H_2SO_4 (0.4)	8	57.2	3.4	37.0	2.4	0.94
6	H_3PO_4 (0.6)	8	25.9	3.3	65.0	5.8	0.92
7	$ZnCl_2$ (0.4)	4	75.5	0.1	9.8	14.6	0.40

First, we determined the relationship between reflux temperature and selectivity ratio using *p*-toluenesulfonic acid(run 1 in Table 2). The removal of water from reaction medium by azeotropic dehydration is essential for these products. The solvents affected the ratio noticeably, and it was much higher in benzene(0.95) than in toluene(0.90), whereas the by-production of dimer (**6**) could not be reduced. Next, an investigation of various acids in refluxing benzene was made. Many acids employed showed the selectivity ratio of **2**/(**2**+**5**) over 0.9 except for zinc chloride. The experiments showed that the reaction was progressed most quickly when azeotropic dehydration was performed using methanesulfonic acid (MSA) or *p*-toluenesulfonic acid (PTS). In respect of the byproducts (**5**) and (**6**), methanesulfonic acid reduced the by-production of them most effectively, and the maximum effect was observed when equivalent amount of the acid to the substrate (**3**) was used. From the above results, the target (**2**) is available at almost quantitatively by using methanesulfonic acid as an acid catalyst in the amount equimolar to the benzophenone (**3**), and performing azeotropic dehydration in benzene.

EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus MP-500V and uncorrected. IR spectra were measured (in Microporous Polyethylene Film, 3M IR Cards Type 61-100-12) on a Horiba Fourier Transform Infrared Spectrometer FT-210 and Spectradesk SD-20. NMR spectra were obtained on a Varian INOVA-400 instrument with TMS as the internal standard. MS spectra were recorded on a JEOL JMS-SX-102A spectrometer. Elemental analysis was performed with a Perkinelmer CHN-2400. The molar percent of compounds was determined by HPLC(ODS 4.6X250 mm, CH_3CN : H_20=8 : 2, 1.0 mL/min, 40°C, 254 nm).

Synthesis of ethyl 2-cyclopropyl-4-(4'-fluorophenyl)quinoline-3-carboxylate(2)

In 2800 mL of molecular sieve dehydrated benzene, 280.0 g (1.30 mol) of **3** and 213.3 g (1.37 mol) of **4** were suspended. With stirring, 125.0 g (1.30 mol) of methanesulfonic acid was added to the suspension. Methanesulfonate salt of **3** was deposited and the suspension turned to white.[9] The mixture was refluxed for 10 h for azeotropic dehydration with a Dean-Stark trap. After confirming the disappearance of **3**, 500 mL of water was added and cooled to 50 °C. The resulting solution was neutralized with a solution containing 61.5 g of NaOH in 500 mL of water. After separation, the organic layer was washed twice with 700 mL of water. 10 g of activated charcoal was added and filtered on a celite bed. The celite bed was washed with 700 mL of benzene, and the washings were combined with the filtrate. 3200 mL of the solvent was evaporated under reduced pressure at a temperature below 50 °C. The solution was diluted with 840 mL of petroleum ether at 30-40 °C. After seeding a small amount of **2**, the solution was cooled to 10 °C and stirred for 1 h. The mixture was cooled to 0 °C and further 840 mL of petroleum ether was added and stirred for 2 h. The precipitated crystals were filtered, washed with 420 mL of petroleum ether and dried at 40 °C under a pressure below 10 mmHg to obtain 413.1 g (94.9 %) of the target (**2**).

2; colorless prisms, mp 73.5-75.5 °C (recrystallized from cyclohexane);

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, 3 H, *J*=7.14 Hz), 1.0-1.1 (m, 2 H), 1.3-1.4 (m, 2 H), 2.2-2.3 (m, 1 H), 4.12 (q, 2 H, *J*=7.14 Hz), 7.17 (br d, 1 H, *J*=8.6 Hz), 7.20 (br d, 1 H, *J*=8.8 Hz), 7.3-7.4 (m, 3 H), 7.48 (br d, 1 H, *J*=8.4 Hz), 7.66 (br dd, 1 H, 7.1 Hz, 8.4 Hz), 7.98 (br d, 1 H, *J*=8.6 Hz); ^{13}C-

NMR (400 MHz, MeOH-d_4) δ: 10.54, 13.87, 15.50, 61.46, 115.37 (2C, d, $^2J_{C\text{-}F}$=21.8 Hz), 125.00, 126.04, 126.12, 127.89, 129.19, 130.08, 131.37 (2C, d, $^3J_{C\text{-}F}$ =8.0 Hz), 131.82 (d, $^4J_{C\text{-}F}$ =3.4 Hz), 144.35, 148.03, 158.38, 162.86 (d, $^1J_{C\text{-}F}$ =248.0 Hz), 168.64; IR (film) 1727.9(s), 1228.4(s) cm^{-1}; MS (FAB) *m/z* 236 (M+1)$^+$; MS (EI) *m/z* 335 (M$^+$), 262 (base); HRMS (EI) found 335.1340, calculated for $C_{21}H_{18}NO_2F$ 335.1322. Anal. Calcd for $C_{21}H_{18}NO_2F$: C, 75.21; H, 5.41; N, 4.18. Found: C, 75.38; H, 5.43; N, 4.12.

Synthesis of 3-cyclopropanecarbonyl-4-(4'-fluorophenyl)-2-quinolone(5)

5 was prepared exclusively at several tens of percent yield in the manner of run 1 in Table 1.

5; colorless needles, mp 263.0-264.5℃(recrystallized from 1-propanol);

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.7-0.9 (m, 4 H), 2.1-2.2 (m, 1 H), 7.1-7.2 (m, 2 H), 7.2-7.6 (m, 6 H), 12.10 (s, 1 H); ^{13}C-NMR (400 MHz, DMSO-d_6) δ: 11.14, 22.63, 115.03 (2C, d, $^2J_{C\text{-}F}$ =21.3 Hz), 115.46, 118.74, 122.07, 126.71, 130.40 (d, $^4J_{C\text{-}F}$ =3.6 Hz), 130.92, 131.16 (2C, d, $^3J_{C\text{-}F}$ =8.0 Hz), 133.85, 138.44, 146.01, 158.99, 161.99 (d, $^1J_{C\text{-}F}$ =245.7 Hz), 203.19; IR (film) 1684.5(m), 1648.8(s) cm^{-1}; MS (EI) *m/z* 307 (M$^+$), 279 (base), 266; MS (FAB) *m/z* 308 (M+1)$^+$, 266; HRMS (EI) found 307.0994, calculated for $C_{19}H_{14}NO_2F$ 307.1009. Anal. Calcd for $C_{19}H_{14}NO_2F$: C, 74.26; H, 4.59; N, 4.56. Found: C, 74.29; H, 4.73; N, 4.46.

Synthesis of 6,12-bis(4'-fluorophenyl)dibenzo[*b*, *f*]-[1, 5] diazocine(6)

In 200 mL of molecular sieve dehydrated toluene, 2.00 g (9.3 mmol) of **3** and 0.35 g (20 mol %) of *p*-toluenesulfonic acid were suspended. After 5-h refluxing with a Dean Stark trap, the solvent was distilled off to dryness at atmospheric pressure. The obtained residue was flash chromatographed on silica gel. Elution with 10 % ethyl acetate / *n*-hexane gave **6** (1.09 g, 29.7 %) as a pale brown powder.

6; colorless plates, mp 177.0-178.5℃(recrystallized from chloroform and *n*-hexane);

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.9-7.0 (m, 2 H), 7.0-7.1 (m, 8 H), 7.3-7.4 (m, 2 H), 7.7-7.8 (m, 4 H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 115.28 (2C, d, $^2J_{C\text{-}F}$ =21.3 Hz), 120.97, 123.51, 126.59, 127.42, 129.80, 131.56 (2C, d, $^3J_{C\text{-}F}$ =8.9 Hz), 134.15 (d, $^4J_{C\text{-}F}$ =2.7 Hz), 151.74, 164.73 (d, $^1J_{C\text{-}F}$ =252.8 Hz), 168.41; IR (film) 1622.8(s), 1586.2(s), 1221.7(s) cm^{-1}; MS (EI) *m/z* 394 (base, M$^+$), 272, 149; MS (FAB) *m/z* 395 (M+1)$^+$, 394 (M$^+$), 299; HRMS (EI) found 394.1314, calculated for $C_{26}H_{16}N_2F_2$ 394.1282. Anal. Calcd for $C_{26}H_{16}N_2F_2$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.16; H, 4.19; N, 7.07.

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