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Tetrahedron 62 (2006) 4065–4070
Tetrahedron

Process development of a disease-modifying antirheumatic drug, TAK-603, based on optimization of Friedel–Crafts reaction and selective substitution of a triazole ring

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Received 28 December 2005; revised 7 February 2006; accepted 8 February 2006

Available online 3 March 2006

Abstract—A practical method for the preparation of **TAK-603**, an antirheumatic drug, has been developed. As a result of optimizing the Friedel–Crafts reaction in the presence of $SnCl_4/POCl_3$, 2-aminobenzophenone skeleton, the key intermediate of **TAK-603**, was formed with good yield. The selective substitution reaction of 1,2,4-triazole was accomplished using 4-amino-1,2,4-triazole and deamination.

1. Introduction

Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (**TAK-603**, Fig. 1) was identified as a disease-modifying antirheumatic drug. In our medicinal chemistry research, some original synthetic routes to **TAK-603** were developed.[1] The latter medicinal synthesis route, as shown in Scheme 1, produced a high-purity product.

However, from the viewpoint of the large-scale preparation of **TAK-603**, which requires further evaluation (e.g., toxicological and clinical studies), the original synthetic method for **TAK-603** has some drawbacks, such as low yield in the formation of the benzophenone derivative **4**, low regioselectivity in the substitution reaction of 1,2,4-triazole with **6**, and repeated tedious chromatography for purification. Here, we present an efficient process established by the optimization of 2-aminobenzophenone skeleton formation via Friedel–Crafts reaction, a selective substitution of 1,2,4-triazole using 4-amino-1,2,4-triazole and avoiding chromatography, as outlined in Scheme 2.

2. Results and discussion

2.1. Optimization of the Friedel–Crafts reaction

As shown in Scheme 1, 2-aminobenzophenone intermediate **4** was derived from *N*-(3,4-dimethoxyphenyl)acetamide **2** and 3,4-dimethoxybenzoic acid **3** using polyphosphoric acid (PPA) at 100 °C. In this method, it only yielded 66% because of side reactions, such as the deacetylation of **2** and demethylation at the 3-position of **3**. In addition, PPA has

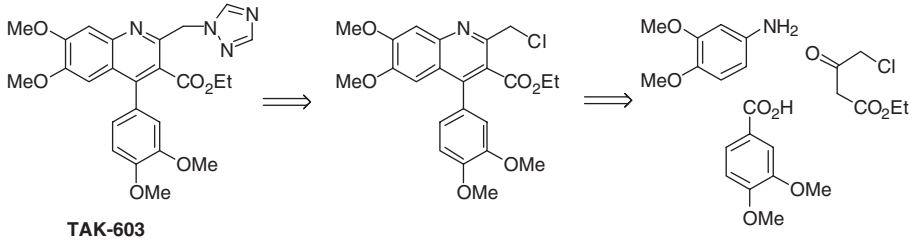

Figure 1.

Keywords: TAK-603; Friedel–Crafts reaction; Selective substitution; 1,2,4-Triazole.
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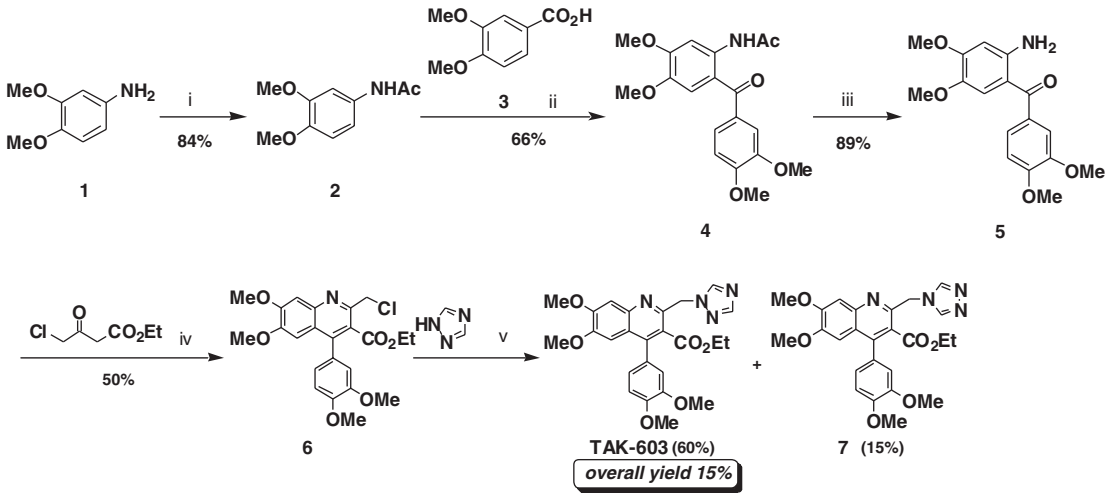
doi:10.1016/j.tet.2006.02.021



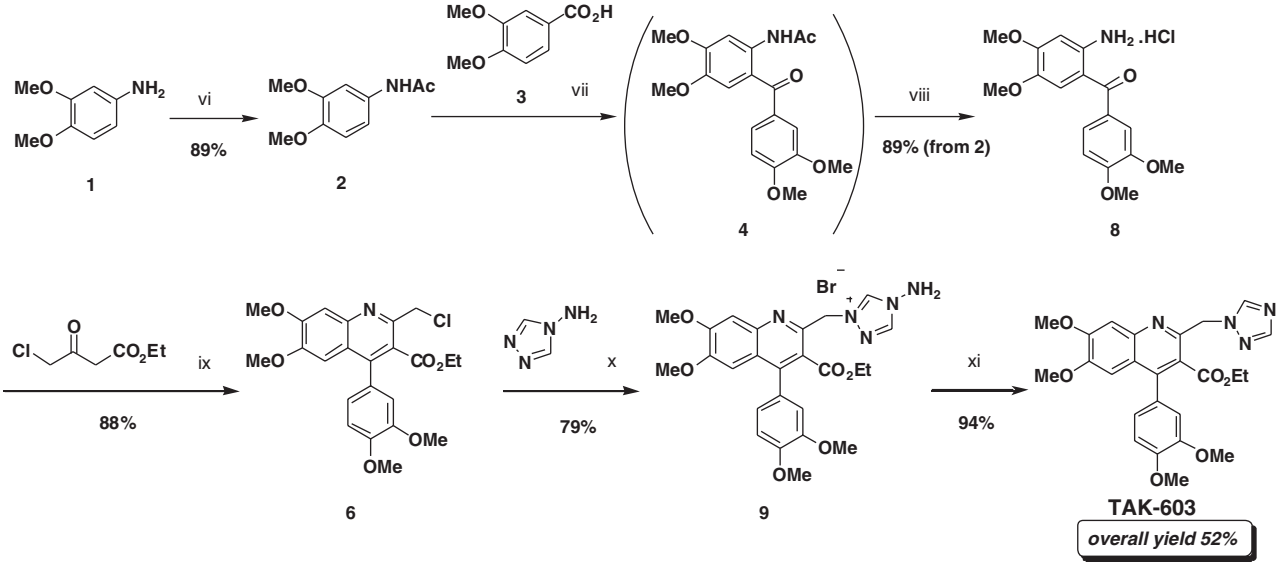
Scheme 1. Reagents and conditions: (i) Ac_2O, pyridine; (ii) PPA, 100 °C; (iii) 6 N HCl, AcOH, reflux; (iv) H_2SO_4, AcOH, 90 °C, then silicagel chromatography; (v) NaH, DMF, 80 °C, then silicagel chromatography.

drawbacks for large scale synthesis because of its viscosity, and significant amounts of water and solvent are needed post-treatment.

To improve these drawbacks, we studied the reaction conditions. In the case of hydroxybenzophenone, it was known that the use of zinc chloride or tin chloride as Lewis acid gave relatively good yield.[2]

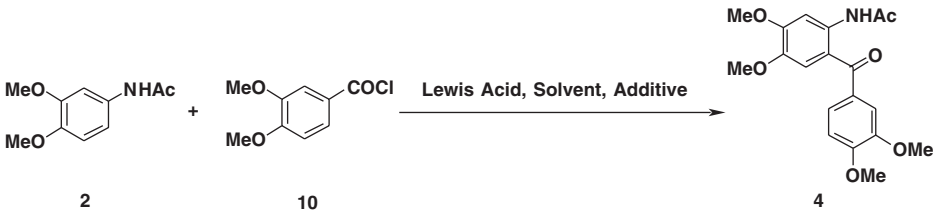
Therefore, we studied Lewis acid and solvents in the reaction of **2** and 3,4-dimethoxybenzoyl chloride **10**, an acid chloride form of **3**, as shown in Table 1. First, we studied Lewis acid as shown in entries 1–4, and established that tin chloride is the best choice. Next, in the presence of tin chloride, we studied solvents as shown in entries 5–11, and established that methylene chloride and ethylene dichloride are excellent solvents; when the 3 equiv of **10** was used in methylene chloride, the yield of **4** was up to 92% (entry 9). This result suggested that more than 1 equiv of **10** was consumed by hydrolysis during the reaction, so the ratio of **10** was fixed at 1.5 equiv to **2**, and we studied the molar ratio of tin chloride and additives as shown in entries 12–17. As a result, the equivalent of tin chloride did not affect the yield of **4**, while an increase in the equivalent of phosphorus oxychloride, which regenerates **10** from **3**, elevated the yield of **4**. In particular, when the 3 equiv of phosphorus oxychloride was used, the yield of **4** was up to 96% (entry 17).

After examining **2** and **10**, we studied the reaction of **2** and **3** in the same way. Optimization of the equivalent of **3**, tin chloride and phosphorus oxychloride was examined as shown in Table 2, and we determined the optimum conditions as shown in entry 4 of Table 2. Thus, we added concd HCl and isobutyl alcohol to the residue of **4** after workup (separation and evaporation) and crystallized to give **8** of high quality and 89% yield based on **2** in two steps.



Scheme 2. Reagents and conditions: (vi) Ac_2O, NaOH, H_2O, 50 °C; (vii) $SnCl_4$, $POCl_3$, CH_2Cl_2, reflux; (viii) concd HCl, EtOH, reflux; (ix) EtOH, reflux; (x) NaBr, DMF, 65 °C; (xi) $NaNO_2$, concd HCl, 5 °C.

Table 1. Study of Lewis acid, solvent and additive; reaction of **2** and **10**



2 10 4

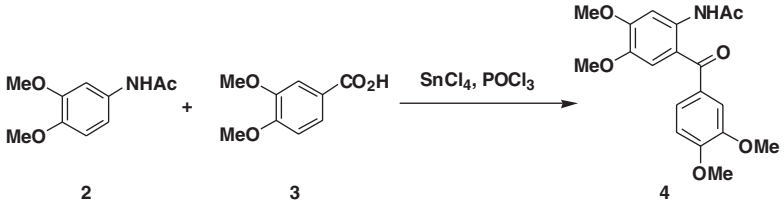
Entry	Lewis acid[a]	Solvent	Molar ratio				Yield of **4** (%)[b]
			2	**10**	Lewis acid	Additive	
1	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	—	62
2	$FeCl_3$	CH_2Cl_2	1.0	2.0	2.0	—	47
3	$CF_3SO_3SiMe_3$	CH_2Cl_2	1.0	1.5	1.1	—	2
4	$TiCl_4$	CH_2Cl_2	1.0	1.5	1.5	—	2
5	$SnCl_4$	THF	1.0	1.5	2.0	—	ND[c]
6	$SnCl_4$	$CHCl_3$	1.0	1.5	2.0	—	34
7	$SnCl_4$	CH_2Cl_2	1.0	1.5	2.0	—	64
8	$SnCl_4$	CH_2Cl_2	1.0	2.0	2.0	—	80
9	$SnCl_4$	CH_2Cl_2	1.0	3.0	3.0	—	92
10	$SnCl_4$	$CH_2(Cl)CH_2Cl$	1.0	1.5	2.0	—	66
11	$SnCl_4$	$CH_3(CH_2)_3Cl$	1.0	1.5	1.5	—	ND
12	$SnCl_4$	CH_2Cl_2	1.0	1.5	2.0	—	64
13	$SnCl_4$	CH_2Cl_2	1.0	1.5	3.0	—	61
14	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$AlCl_3$ (0.1)	63
15	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (0.4)	74
16	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (1.5)	82
17	$SnCl_4$	CH_2Cl_2	1.0	1.5	1.5	$POCl_3$ (3.0)	96

Reaction conditions: CH_2Cl_2-reflux 3–7 h.
[a] We used another Lewis acid (e.g., $AlCl_3$, BF_3/Et_2O, $ZnCl_2$) in $CH_2(Cl)CH_2Cl$, but the yield of **4** was very low.
[b] Isolated yield.
[c] ND, not detected.

2.2. Selective substitution reaction of 1,2,4-triazole

In general, substitution reactions of 1,2,4-triazole produce two regioisomers (N-1 position substitute and N-4 position substitute).[3] Although reaction conditions such as the solvent, temperature or additive were studied to avoid this problem, it was difficult to obtain only one regioisomer. In our preliminary study concerning the reaction of 1,2,4-triazole with **6**, the desired N-1 position substitute was obtained in 60–70% along with about 15% of undesired 4-position substitute as shown in Scheme 1.

Table 2. Reaction of **2** and **3**

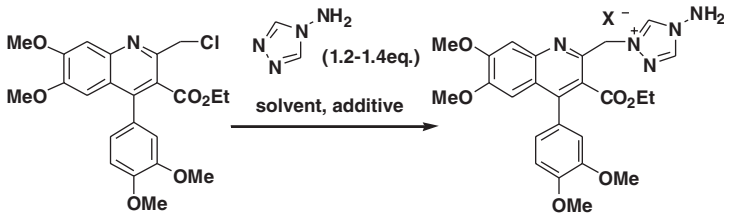


2 3 4

Entry	Molar ratio				Reaction		
	2	**3**	$SnCl_4$	$POCl_3$	Time (h)	Yield of **4** (%)[a]	Ratio by HPLC of **4**[b]
1	1.0	1.1	1.2	8.5	20	68	75
2	1.0	1.1	1.5	8.5	12	87	87
3	1.0	1.1	1.8	5.0	12	83	85
4	1.0	1.1	1.8	5.0	24	94	94
5	1.0	1.1	1.8	8.5	12	93	92
6	1.0	1.3	1.8	8.5	12	99	90
7	1.0	1.5	1.5	8.5	16	84	77
8	1.0	1.5	1.8	8.5	12	96	85
9	1.0	1.5	2.0	8.5	12	97	87

Reaction conditions: CH_2Cl_2-reflux.
[a] Isolated yield.
[b] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.

Table 3. Reaction of **6** with 4-amino-1,2,4-triazole



6 9 (X=Cl, Br, I)

Entry	Solvent	Additive (equiv)	Reaction		Ratio by HPLC[a]	
			Temperature (°C)	Time (h)	**6**	**9**
1	EtOH	—	Reflux	15	46	49
2	*i*-PrOH	—	Reflux	12	58	39
3	MeCN	—	Reflux	15	7	88
4	DMF	—	100	12	0.2	89
5	MeCN	NaBr (1.1)	70	3	35	61
6	DMF	NaBr (1.1)	70	3	0.01	94
7	DMF	NaI (1.2)	70	2	ND[b]	88

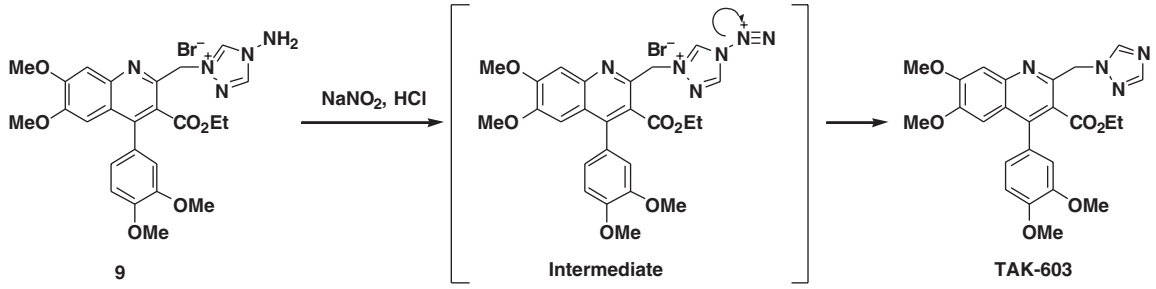
[a] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.
[b] ND, not detected.

Therefore, we investigated an alternative method to obtain the selectively desired regioisomer, which is the N-1 position substitute of 1,2,4-triazole. Some strategies for selective substitution reactions of 1,2,4-triazole are known, for example, the reaction with 1-trimethylsilyl-1,2, 4-triazole or 1-tributyltin-1,2,4-triazole,[4] isomerization at high temperature,[5] and reaction with 4-amino-1,2, 4-triazole.[6] The former two methods[4,5] require a high temperature (150–180 °C), so we chose the method using 4-amino-1,2,4-triazole. Although the alkylation of 4-amino-1,2, 4-triazole proceeded easily in polar media (isopropyl alcohol, or acetonitrile) exclusively at the N-1 position with good yield with alkyl halides, only small molecules have been identified such as benzyl, benzoylmethyl, 2,4-dichlorobenzoylmethyl and so on.[6] The resulting aminotriazolium salts were deaminated readily with a slight excess of nitrous acid in an essentially quantitative yield.

Our substrate is a relatively large molecule (MW 446), so this is the first application with a large molecular compound. First, as shown in Table 3, we studied solvents, additives and reaction temperatures, and found that dimethylformamide (DMF) is the best solvent compared with other solvents (isopropyl alcohol, or acetonitrile) in the literature.[6] We also discovered that the addition of sodium bromide or sodium iodide was effective in improving the reaction rate. After our studies, we determined the reaction conditions as shown in entry 6 of Table 3, and high quality triazolium salt **9** was obtained containing sodium chloride. Although the deamination of **9** without isolation is possible, we isolated **9** from ethyl acetate as crystals because of the qualification of the product.

After the isolation of triazolium salt **9**, we studied the deamination reaction following the literature method.[6] In the acidic condition at 3 °C, after the solution of sodium nitrite was added gradually for 10 min, the deamination reaction progressed immediately as shown in Table 4. After gradually warming to room temperature for 60 min, the

Table 4. Deamination reaction of **9**



9

Reaction		Ratio by HPLC[a]		
Time (min)	Temperature (°C)	**9**	Intermediate	**TAK-603**
0	3	11	7	79
15	13	ND[b]	4	96
30	20	ND	1	98
60	25	ND	0.2	99

[a] Determined at 254 nm, YMC A-302 column, 50 mM KH_2PO_4/MeCN=55:45.
[b] ND, not detected.

reaction proceeded quantitatively. We speculate that the intermediate, observed on HPLC, is *N*-diazonium salt[7] as shown in Table 4.

2.3. Other improvements for process development

In order to develop a large scale practical preparation, other improvements have been made as shown in Scheme 2 against the former method as shown in Scheme 1, with the exception of the descriptions mentioned above. Concerning the N-acylation reaction, which produces **2** from **1**, sodium hydroxide was used as the base in the water solution instead of pyridine in the methylene chloride solution. Following this modification, it was able to precipitate **2** from the reaction mixture and omit the separation. Concerning the quinoline ring closure reaction, which produces **6**, after refluxing hydrochloride salt **8** in ethanol and the addition of triethyl amine, **6** was precipitated from the reaction mixture. Following this modification, it was able to avoid the chromatographic purification.

3. Conclusion

In conclusion, we have developed a large scale practical preparation method of **TAK-603** based on two main improvements, for example, the optimization of the Friedel–Crafts reaction and the selective substitution reaction of 1,2,4-triazole. Following our new procedure, multikilogram quantities of the bulk substance for toxicological and clinical studies have been prepared without requiring chromatographic purification.

4. Experimental

4.1. General

Melting points were determined on a Yanagimoto micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian Gemini-200 spectrometer. ^{1}H chemical shifts were referenced to the internal deuterated solvent or tetramethylsilane. Elemental analysis were performed at Takeda Analytical Research Laboratories, Ltd. All commercial chemicals and solvents used were reagent grade and were used without further purification.

4.1.1. *N*-(3,4-Dimethoxyphenyl)acetamide (2). To a suspension of 3,4-dimethoxyaniline (**1**, 50.0 kg) in water (420 L) were alternately added a one-fifth portion of a solution (100 L) of sodium hydroxide (17.0 kg) in water and a one-fifth portion of acetic anhydride (43.3 kg) at less than 65 °C with stirring. After stirring for 20 min at 55–60 °C, the reaction mixture was cooled to about 5 °C and stirred for 1 h to precipitate crystals. The resulting crystals were collected by filtration, washed with water (200 L) and then dried at 50–60 °C for 7 h to give **2** (56.8 kg, yield 89%): mp 130–131 °C; IR (KBr): 1658, 1607, 1520, 1258, 1238 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.79 (d, J=8.4 Hz, 1H), 6.85 (dd, J=8.4, 2.0 Hz, 1H), 7.11 (br s, 1H), 7.30 (d, J=2.0 Hz, 1H).

4.1.2. 2-Acetylamino-3′,4,4′,5-tetramethoxybenzophenone (4). 3,4-Dimethoxybenzoic acid (**3**, 20.0 kg) was added to a suspension of **2** (19.6 kg) in polyphosphoric acid (20.5 kg) with stirring, the mixture was heated at 95–110 °C for 3 h, and then allowed to stand overnight at room temperature. To the mixture was added ice (30 kg) and cold water (500 L, 0–5 °C) at less than 80 °C with stirring and the mixture was extracted with ethyl acetate (530 L, 210 L×2). The extracts were combined and washed with a solution of sodium hydroxide (42.5 kg) in water (500 L) and concentrated in vacuo. After *n*-heptane (200 L) was added to the resulting residue, the mixture was stirred for 1 h at about 5 °C to precipitate crystals. The resulting crystals were collected by filtration, washed with a mixture of ethyl acetate (6 L) and *n*-heptane (24 L) and then dried at room temperature for 95 h to give **4** (23.6 kg, yield 66%): mp 129–130 °C; IR (KBr): 1693, 1610, 1590, 1529, 1518, 1270 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.76 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 6.92 (d, J=8.8 Hz, 1H), 7.08 (s, 1H), 7.27–7.34 (m, 2H), 8.38 (s, 1H), 11.04 (s, br s).

4.1.3. 2-Amino-3′,4,4′,5-tetramethoxybenzophenone hydrochloride (8) from 4. Hydrochloric acid (35%, 180 L) was added to a solution of **4** (50.7 kg) in *i*-butanol (600 L) and the mixture was refluxed for 2 h with stirring. The reaction mixture was cooled and allowed to stand overnight at room temperature and the mixture was stirred for 1 h at about 5 °C. The resulting crystals were collected by filtration, washed with *i*-butanol (180 L) and then dried in vacuo at 30–40 °C for 10 h to give **8** (46.8 kg, yield 94%): mp 172–173 °C; IR (KBr): 3430, 3305, 1621, 1590, 1535, 1510, 1250 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 6.01 (br s, 2H), 6.22 (s, 1H), 6.90 (d, J=8.6 Hz, 1H), 7.02 (s, 1H), 7.21–7.30 (m, 2H).

4.1.4. 2-Amino-3′,4,4′,5-tetramethoxybenzophenone hydrochloride (8) via 4 from 2. To a suspension of **2** (195.2 g) and **3** (200.4 g) in methylene chloride (800 mL) were added phosphorus oxychloride (766.6 g) and tin chloride (469.0 g) at less than 40 °C. After stirring for 24 h at 49 °C, methylene chloride (2 L) was added to the reaction mixture and cooled to about 10 °C. To the mixture was added water (5 L) at less than 35 °C with stirring and the mixture was extracted. The extract was washed with a solution of sodium hydroxide (60 g) in water (1.94 L) and water (2 L), and then concentrated in vacuo. After hydrochloric acid (35%, 1.154 L) and *i*-butanol (3.86 L) were added to the resulting residue, the mixture was stirred for 2 h at about 75 °C, and then the reaction mixture was stirred for 2 h at about 10 °C. The resulting crystals were collected by filtration, washed with *i*-butanol (1.16 L), and then dried in vacuo at 45 °C for 10 h to give **8** (314.9 g, yield 89% in two steps).

4.1.5. Ethyl 2-chloromethyl-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (6). Ethyl 4-chloroacetoacetate (11.1 kg) was added to a solution

of **8** (18.1 kg) in ethanol (177 L) and the mixture was stirred for 3 h at 77–80 °C. After cooling, triethylamine (5.3 kg) was added to the reaction mixture and the mixture was stirred for 1 h at 5–15 °C. The resulting crystals were collected by filtration and washed with ethanol (35 L). The crystals were dissolved in dichloromethane (75 L) and the solution was washed with water (60 L×2) and concentrated in vacuo. Ethanol (50 L) was added to the residue and the solution was concentrated in vacuo to remove the residual dichloromethane. Ethanol (50 L) was added to the residue to precipitate crystals. The resulting crystals were collected by filtration, washed with ethanol (35 L) and then dried in vacuo at 40 °C for 8 h to give **6** (20.1 kg, yield 88%): mp 142–143 °C; IR (KBr): 1719, 1518, 1500, 1461, 1425, 1258 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.02 (t, J=7.2 Hz, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 4.10 (q, J=7.2 Hz, 2H), 4.92 (d, J=11.0 Hz, 1H), 4.99 (d, J=11.0 Hz, 1H), 6.90–7.03 (m, 4H), 7.46 (s, 1H); Anal. Calcd for $C_{23}H_{24}NO_6Cl$: C, 61.95; H, 5.43; N, 3.14. Found: C, 61.92; H, 5.42; N, 2.90.

4.1.6. 4-Amino-1-[4-(3,4-dimethoxyphenyl)-3-ethoxycarbonyl-6,7-dimethoxyquinolin-2-ylmethyl]-4*H*-1,2,4-triazolium bromide (9). 4-Amino-1,2,4-triazole (5.0 kg) and sodium bromide (5.0 kg) were added to a suspension of **6** (19.6 kg) in *N*,*N*-dimethylformamide (43 L) and the mixture was stirred for 5 h at 63–67 °C. To the reaction mixture was added ethyl acetate (93 L) and the mixture was stirred for 1 h at 5–15 °C. The resulting crystals were collected by filtration, washed with ethyl acetate (176 L) and then dried in vacuo at 40 °C for 8 h to give **9** (20.0 kg, yield 79%): mp 183–184 °C; IR (KBr): 3196, 1706, 1518, 1472 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 0.92 (t, J=6.9 Hz, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 3.72–4.09 (m, 2H), 5.94 (s, 2H), 6.93–7.31 (m, 7H), 9.28 (s, 1H), 10.41 (s, 1H); Anal. Calcd for $C_{25}H_{28}N_5O_6$-$Br(0.7H_2O)$: C, 51.15; H, 5.05; N, 11.93. Found: C, 51.10; H, 4.91; N, 11.88.

4.1.7. Ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(4*H*-1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (TAK-603). To a suspension of **9** (20.0 kg) in water (267 L) were added hydrochloric acid (36%, 7.8 kg) and a solution of sodium nitrite (3.1 kg) in water (78 L) at less than 5 °C. After stirring for 3 h at 23 °C, the reaction mixture was adjusted to pH 6.7 with a solution of sodium hydroxide (3.1 kg) in water (15 L) at 10–20 °C. Acetone (73 L) was added to the mixture and the resulting crystals were collected by filtration, washed with a mixture of acetone (15 L) and water (76 L), and then dried in vacuo at 40 °C for 8 h to give **TAK-603** (15.7 kg, yield 94%): mp 174–175 °C; IR (KBr): 1719, 1519, 1502, 1463, 1258 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J=7.2 Hz, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.95 (q, J=7.2 Hz, 2H), 3.97 (s, 3H), 4.06 (s, 3H), 5.74 (s, 2H), 6.80–7.02 (m, 4H), 7.42 (s, 1H), 7.94 (s, 1H), 8.28 (s, 1H); Anal. Calcd for $C_{25}H_{26}N_4O_6$: C, 62.75; H, 5.48; N, 11.71. Found: C, 62.77; H, 5.52; N, 11.48.

Acknowledgements

The authors thank Dr. Kiminori Tomimatsu and Messrs. Kokichi Yoshida and Mitsuhisa Yamano for helpful discussions.

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7. Generally, aromatic diazonium salts are stable as a solid and have explosive characteristics. In contrast to this, *N*-diazonium salts are unstable and there is no literature about their isolation and/or explosive nature.