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Scalable Synthesis of 8-Amino-3-hydroxy-6*H*-benzo[*c*]chromen-6-one: Key Intermediate for SEGRA via the Hurtley Reaction

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ABSTRACT: A practical and scalable process for the preparation of 8-amino-3-hydroxy-6*H*-benzo[*c*]chromen-6-one in multihundred kilogram amounts has been developed. The key features of this synthesis are the application of the Hurtley reaction with a copper and base combination and the development of a purification process. The new synthesis improved the total yield from 49.0% to 59.5% and reduced the number of steps from three to two. Compared with the conventional medicinal route, manufacturing costs were reduced significantly by the use of inexpensive, easy to procure materials.

INTRODUCTION

Glucocorticoids (GC) play a dominant role in the treatment of inflammatory conditions. Apart from their potent anti-inflammatory activity, long-term, and high dose treatment may lead to serious adverse effects. It has been hypothesized that transrepression (TR) is the basis of their anti-inflammatory effects, whereas transactivation (TA) has been assumed to cause their side effects.[1]

In recent years, a selective glucocorticoid receptor agonist (SEGRA) that can separate TR and TA activities without a steroid framework was reported.[2] SEGRA compounds (Figure 1) exert selective TR and exhibit a similar GR binding potency

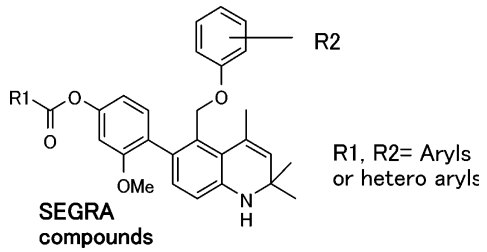

Figure 1. General structure of SEGRA compounds.

to that of dexamethasone in vitro. In an in vivo assay, SEGRA compounds showed a remarkable anti-inflammatory effect after topical dosing to the eye and side effect dissociation.[3] To evaluate efficacy in preclinical studies and clinical trials, multikilogram quantities of SEGRA compounds were required. Consequently, the development of a reliable and cost-effective synthesis process with high yield was important.

In the conventional medicinal route (Scheme 1),[3c] a number of SEGRA compounds were synthesized from key intermediate **1a**. Synthesis of **1a** was conducted in a three-step procedure that involved the Suzuki−Miyaura coupling of commercially available **2** and **3** in quantitative yield. Cleavage of the methyl ether of **4** with BBr_3 and successive intramolecular cyclization provided **5**, which has 3-hydroxy-6*H*-benzo[*c*]chromen-6-one framework, in 51% yield. The nitro moiety of **5** was reduced to give **1a** in 96% yield. In this synthesis, **1a** was obtained in three steps with a total yield of 49%. However, manufacturing costs in this process are extremely high, and there are serious environmental concerns due to the use of 5 mol % of palladium catalyst and the extensive use of boronic acid **2** and BBr_3/CH_2Cl_2.[4a,b]

Therefore, a more economical synthetic route for **1a** is desirable.

In synthetic approaches for the key intermediate **1a**, the Hurtley reaction, which is a one-pot condensation of phenols and 2-halobenzoic acid in the presence of a copper catalyst, is considered to be appropriate.[5] Although resorcinol **7** and copper catalyst would be cost-effective and the number of steps would be reduced, few examples of the reaction of nitro or amino analogues on the 5-position of bromobenzoic acid **6** have been reported, and there have been no reports of such a reaction with high yield (Scheme 2).[6] In this study, we investigated a practical and scalable synthesis of **1a** via the Hurtley reaction.

RESULTS AND DISCUSSION

To investigate feasibility, the Hurtley reaction was assessed in the reaction of 5-amino-2-bromobenzoic acid **6a** (Table 1). A reaction of **6a** was found to give trace amounts of **1a** in 30 min (entry 1). A significant number of byproducts occurred with the use of a free amino substituent; consequently, it was considered that improving the yield would be difficult. It was found that acetyl protection of the amino substituent to give **6b** was affordable and that this compound was readily available in large quantities. When the reaction with **6b** was conducted, **1b** was isolated by filtration (39% yield) with fewer byproducts than in entry 1 (entry 2). When the amount of reagents was increased (3.0 equiv of **7**, 3.3 equiv of NaOH, and 0.3 equiv of $CuSO_4$) the yield improved to 50% (entry 3). For temperature screening at 40 and 60 °C, a superior yield was obtained at 60 °C (entry 4, 5). When the reaction was performed with a

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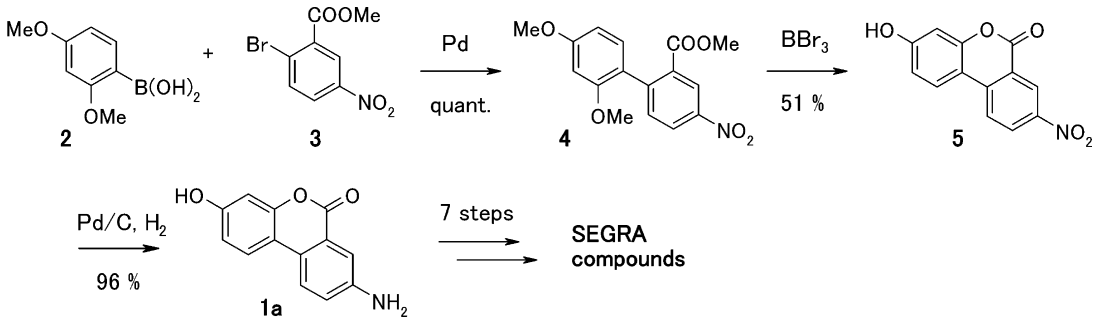
Scheme 1. Initial medicinal route for key intermediate 1a



Scheme 2. New synthetic route of 1 by the Hurtley reaction

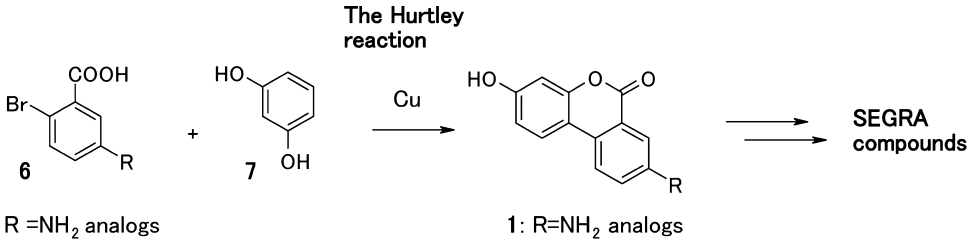
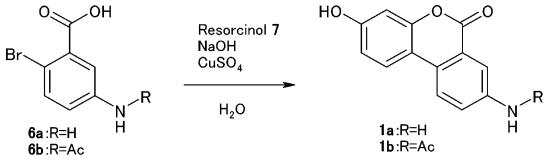


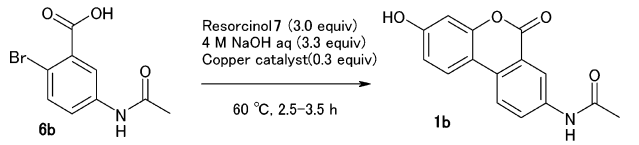
Table 1. Optimization of the Hurtley reaction of 6a, 6b



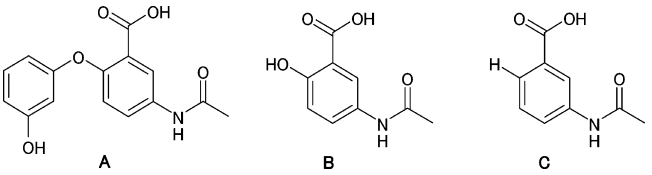
entry	R	temp (°C)	time (h)	resorcinol 7 (equiv)	NaOH (equiv)	$CuSO_4$ (equiv)	yield of 1a, 1b (%)[a,b]
1	H	100	0.5	2.0	2.2	0.10	trace[c]
2	Ac	100	0.5	2.0	2.2	0.10	39
3		100	1	3.0	3.3	0.3	50
4		60	1	3.0	3.3	0.3	65
5		40	3	3.0	3.3	3.0	44
6		60	2	2.0	3.3	0.3	54
7		60	5	3.0	2.0	0.3	32
8		60	3	3.0	3.3	0.05	41
9		60	3	3.0	3.3	0.1	44
10		60	1.5	3.0	3.3	0.5	64

[a]Isolated yield after filtration and washing with 6 M HCl aq, H_2O, and EtOH. [b]All yields excluded resorcinol 7 that was not purified; no other impurities were confirmed by ^1H NMR. [c]After reaction, a trace amount of target materials was observed in crude material by ^1H NMR.

Table 2. Optimization of the copper catalyst and main impurities



entry	catalyst	yield of 1b (%)[a,b]	yield of A (%)[c]	yield of B (%)	yield of C (%)
1	$CuSO_4$[d]	65	13	16	3
2	CuBr	58	13	16	6
3	$Cu(OAc)_2$	57	15	17	5
4	$CuCl_2$	60	16	16	5
5	CuI	67	10	12	2



[a]Isolated yield after filtration and washing with 6 M HCl aq and H_2O. [b]All yields excluded resorcinol 7 that was not purified; no other impurities were confirmed by ^1H NMR. [c]The yields of impurities were confirmed by HPLC assay in the filtrate after filtering off precipitated target material **1b**. [d]This entry was referred from entry 3 in Table 1.

decreased amount of resorcinol 7 and NaOH at 60 °C, the yield decreased (entry 6, 7). When screening for the amount of $CuSO_4$, a lower equivalent resulted in low yield (entry 8, 9), and increasing the amount did not improve the yield (entry 10). The deactivation of the copper catalyst in lower equivalents was considered. It was thought that activity may have been suppressed by the generated solid, and consequently, the activity was reduced as the reaction progressed.

Further investigation was undertaken to determine how the copper counterion effect of the copper catalysts affected yield and byproducts (A, B, and C),[7] as shown in Table 2. It was found that the instability and low yield of the Hurtley reaction primarily arose from the production of the byproducts. When the reaction was performed using CuBr, $Cu(OAc)_2$, and $CuCl_2$ (entry 2, 3, 4), the yields were slightly lower than when $CuSO_4$ (entry 1) was used with similar byproduct profiles. CuI resulted in a slightly higher yield as a consequence of the reduced generation of all byproducts (entry 5). In this screening, the copper counterions did not affect the yield significantly; however, the copper counterion may have influenced the ratio of byproducts.

The results of base screening are presented in Table 3. Compared to NaOH, KOH and LiOH (entry 1, 2) resulted in almost equal yields with similar byproduct profiles. Despite being weak bases, K_2CO_3 and Na_2CO_3 improved the yield slightly (entry 3, 4). Hydroxide bases inhibited the production

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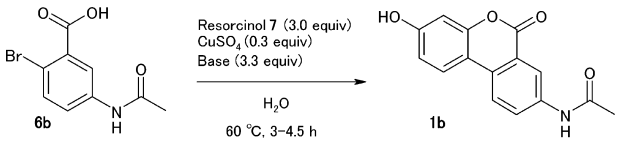
Table 3. Optimization of the base



entry	base	yield of **1b** (%)[a,b]	yield of A (%)	yield of B (%)	yield of C (%)	remaining **6b** (%)
1	KOH	61	14	17	5	
2	LiOH	59	13	19	5	
3	K_2CO_3	65	3	7	11	
4	Na_2CO_3	67	5	6	13	
5	Li_2CO_3	48	11	13	15	2
6	$NaHCO_3$	59	9	11	10	6
7	Et_3N	43	14	25	11	7

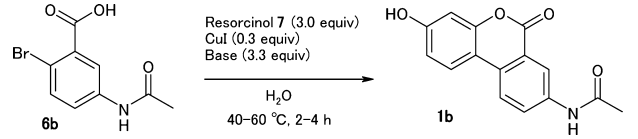
[a]Isolated yield after filtration and washing with 6 M HCl aq and H_2O. [b]All yields excluded resorcinol **7** that was not purified; no other impurities were confirmed by ^1H NMR except for **6b**.

of byproduct C, and carbonate bases inhibited the production of A and B but did not inhibit the production of C. Li_2CO_3 (entry 5) afforded lower yields but resulted in the production of greater amounts of byproducts A and B than those observed for K_2CO_3 and Na_2CO_3. $NaHCO_3$ showed an approximately equivalent yield with comparable production of byproducts A, B, and C and the remaining starting material (entry 6). Et_3N showed relatively low yields with relatively large amounts of byproducts A and B and the remaining starting material (entry 7).

From the results of the investigation to this point, it was found that the Hurtley reaction was able to afford the target material in approximately 65% yield by protecting the amino function with an acetyl group and by increasing the amount of reagents. To achieve further improvement, we focused on profiling the byproducts using different copper and base combinations. Yield was not improved when carbonate bases were used; however, the ratios of byproducts A and B were reduced. With CuI, a drastic reduction of byproduct C was observed. Given these results, combined use of a carbonate base and CuI was explored.

Table 4 shows the results of the Hurtley reaction with CuI and a carbonate base. At 60 °C, 73% yield was obtained with CuI and Na_2CO_3 (entry 1), and all byproducts were reduced. At 50 °C, the yield was greater than 80% (entry 2), and at 40 °C the yield slightly decreased, and a small amount of starting material remained (entry 3). It was found that the initial addition of 1 equiv of NaOH aq to bromobenzoic acid to obtain the corresponding sodium carboxylate and the addition of 2.3 equiv of Na_2CO_3 later in the reaction resulted in an assay yield of 82% (entry 4). These separate additions avoided the foaming that is generated by mixing benzoic acid and a carbonate base, which is a consideration for a scaled-up synthesis. K_2CO_3 resulted in a slightly lower assay yield as compared with case when Na_2CO_3 (entry 5) is used. There is no significant difference between K_2CO_3 and Na_2CO_3; however, Na_2CO_3 is more favorable as it has a lower molecular weight. Li_2CO_3 resulted in low yield and increased byproducts A and B (entry 6). Cs_2CO_3 also resulted in low yield, increased C, and 15% remaining starting material (entry 7). $NaHCO_3$ resulted in relatively low yield (entry 8) with relatively low ratios of byproducts. Use of $KHCO_3$ decreased the yield and showed increased amounts of B and C (entry 9).

Table 4. Optimization of the base and copper catalyst of the Hurtley reaction



entry	temp (°C)	base	yield of **1b** (%)[a,b]	yield of A (%)	yield of B (%)	yield of C (%)	remaining **6b** (%)
1	60	Na_2CO_3	73	6	7	6	
2	50	Na_2CO_3	82[c]	5	7	5	
3	40	Na_2CO_3	79	4	6	4	2
4	50	Na_2CO_3/NaOH	82[c]				
5	50	K_2CO_3	78[c]	4	6	6	
6	50	Li_2CO_3	47	10	15	7	
7	50	Cs_2CO_3	50	4	9	13	15
8	50	$NaHCO_3$	73	5	7	7	4
9	50	$KHCO_3$	55	6	14	17	

[a]Isolated yield after filtration and washing with 6 M HCl aq and H_2O and no further purification to remove CuI. [b]All yields excluded resorcinol **7** that was not purified; no other impurities were confirmed by ^1H NMR except for **6b**. [c]HPLC assay yield.

Possible reasons for the high yield resulting from the combination of CuI and a carbonate base were considered. Here it was thought that a weak base was not sufficient to achieve carbon−carbon and carbon−oxygen bond formation in this reaction. Consequently, the addition of the phenolic hydroxyl group on resorcinol **7** and hydroxide to the substrate was thought to result in reduced amounts of A and B and lead to increased decomposition of the bromide, which resulted in C. In contrast, monovalent CuI had a strong potential to form carbon−carbon and carbon−oxygen bonds,[8] and consequently, the ratio of decomposition was decreased. It was assumed that, compared with conventional the Hurtley reactions, the combination of CuI and a carbonate base improved catalytic activity and reduced byproducts.

To achieve effective synthesis of SEGRA compounds, the removal of copper was important because it was found that residual copper (>900 ppm) showed a critical influence in the subsequent step.[9] However, removing copper was found to be difficult in a large-scale process. At a small scale (100−200 g), washing the target material, which was filtered after the reaction, in an aqueous ammonia slurry for 3 h reduced the amount of residual copper to less than 50 ppm.[10] However, for relatively large-scale synthesis (5 kg), after washing for 3 h, the amount of residual copper was greater than 5000 ppm, and if washing time was extended, a longer filtration time was required because grain refining caused clogging of the filter. To meet large-scale manufacturing requirements, a more effective scalable method was investigated.

Although it was found that **1b** was difficult to solve in various solvents, our investigation revealed that **1b** could be solved in 4 M NaOH aq (5 v/w) and H_2O (20 v/w) at 60 °C. Here, it was assumed that sodium salt **8** was formed, which resulted in the ring opening of the lactone (Scheme 3).[11] Copper salt did not solve in this solution and was removed by filtration.[12] In addition, it was found that **8** in the filtrate solution was easily cyclized under acidic conditions (HCl aq) and afforded **1b**. With regard to the suspension at end of the Hurtley reaction, it was found that adding 4 M NaOH aq and H_2O at 60 °C to the

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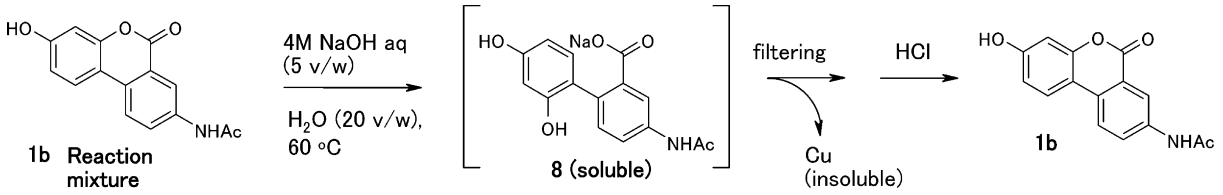
Scheme 3. Copper removal process by forming soluble 8



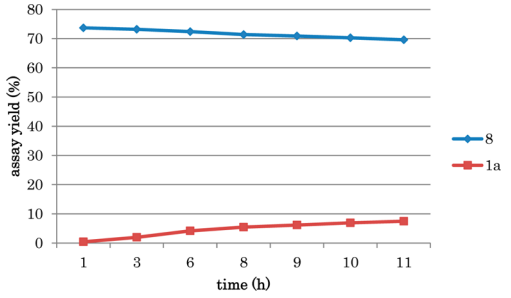
reaction suspension was also able to solve all components other than copper, which could be removed by cellulose powder pad filtration.[13] In 100 kg scale manufacturing, it was confirmed that residual copper is 4 ppm. Thus, **1b** was obtained under acidic conditions.

Byproducts A, B, and C are soluble in acidic filtering solutions and can be easily removed. The unreacted resorcinol **7** reagent, which caused discoloration, was removed by adding MeCN (2−2.5 v/w). Residual Na_2CO_3 was removed under acidic conditions and emitted as CO_2; however, as mentioned previously, prudent addition is necessary to avoid the foaming that is associated with large-scale manufacturing processes. Compared with slurry washing, this purification process is more favorable because it is not easily influenced by scale.

To establish a robust process, it is important to maintain the state of the solution. In the reversible reaction of **1b** and **8**, **1b** was much more dominant than **8**. If a sufficiently dissolved state was not maintained, the loss of yield was observed resulting from the precipitation of insoluble **1b**.

For large-scale production, using cellulose powder pad filtration was expected to take a long time. Therefore, it is necessary to determine the effect of filtration time. Solubility in relation to time and assay yield was investigated (Chart 1).

Chart 1. Time dependence of assay yield of 8 in reaction mixture after adding 4 M NaOH (5 v/w) and H_2O (20 v/w) at 60 °C

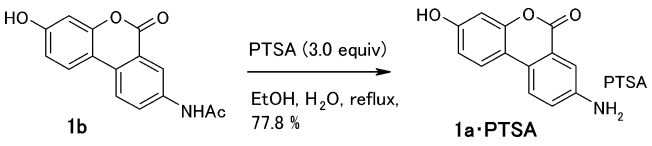


With regard to solubility after the reaction, assay yield was maintained at more than 70% for 10 h.[14] It was observed that the loss of assay yield was not caused by precipitation of **1b** but was a result of deacetylation of **1a**. **1a** is a target product in the deacetylation step, and including **1a** is not critical issue. It was desirable not to change the filtration property in filtering **1b** by including **1a** because **1a** showed poor filterability.

On the basis of the results to this point, high volume manufacture of compound **1a** was undertaken. In the Hurtley reaction with 130 kg of **6b**, followed by subsequent purification, it was found that this procedure provided **1b** in 76.5% yield with 93.6% purity (resorcinol **7**: 2.4%, **1a**: 3.4%, impurity A: N.D., impurity B: 0.19%, impurity C: 0.24%, others: 0.22%) with 4 ppm residual copper.

The acetyl protecting group could be efficiently removed by treating **1b** with 4-toluenesulfonic acid (PTSA) in EtOH/H_2O to provide the desired **1a**·PTSA in 77.8% yield with 99.95% purity (Scheme 4). Conversion of this reaction was

Scheme 4. Deacetylation step by PTSA



quantitative, and there is no impurity; however, the loss of **1a** in the filtrate solution was observed in the crystallization step. PTSA is used as a reagent in the next step,[9] and it was confirmed that, rather than adding 1 equiv of PTSA, **1a**·PTSA was able to affect the reaction. **1a**·PTSA also improved the filtration property compared with free **1a**. In addition, **1a**·PTSA, acted as both a deacetylation reagent and a salt in the subsequent step. A total of 118.9 kg of **1a**·PTSA was prepared in two steps with 59.5% yield.

Compared with the original medicinal synthesis route, a new route via the Hurtley reaction reduced the number of steps by one and improved the total yield from 49.0% to 59.5%. In addition, reagent cost is reduced from USD3057 to USD196 for manufacturing 1 kg of **1a** (Table 5), and the cost of starting materials is also reduced.[4b]

CONCLUSION

We developed an efficient synthetic method to improve the Hurtley reaction by using a combination of CuI and Na_2CO_3 with 5-acetamido-2-bromobenzoic acid. It was revealed that the complementary effect of CuI, which had high intermolecular cross coupling activity that inhibited the production of byproducts because of coupling and the presence of Na_2CO_3, led to improved yields of **1b**. Removal of residual copper after the reaction was achieved by filtration with a ring opening sodium salt **8** that solves in H_2O. Sodium salt **8** was easily closing by acidic conditions and gave **1b** with 4 ppm residual copper. Successful deprotection was achieved by PTSA and afforded **1a**. Because of these improvements, **1a**·PTSA synthesis was achieved in two steps with 59.5% yield. The cost was drastically decreased by replacing the Pd catalyst with Cu, using boronic acid rather than resorcinol **7** as the substrate, and omitting BBr_3 in the demethylation.[4] In addition, this new reaction condition was achieved in a multihundred kilogram scale. Optimization of the Hurtley reaction led to a practical and scalable synthesis that was more cost-effective and less labor intensive.

EXPERIMENTAL SECTION

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. ^1H

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Table 5. Comparison of cost of reagents in medicinal route and new route

	one step		two step		three step	
		cost for **1a** (USD/kg)		cost for **1a** (USD/kg)		cost for **1a** (USD/kg)
medicinal route	K_2CO_3	15	BBr_3	1756	10% Pd/C	210
	$Pd_2C1_2(PPh_3)_2$	1041			H_2	35
	subtotal	1056		1756		245
	total					3057
new route	resorcinol **7**	29	PTSA·H_2O	149		
	Na_2CO_3	1				
	CuI	17				
	subtotal	47		149		
	total					196

NMR spectra were recorded on a JEOL GSX400 or on a JEOL ECP500 spectrometer at ambient temperature. Chemical shifts are reported as ppm downfield from tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons.

HPLC analyses were conducted on a Waters alliance series or Hitachi LaChrom series. C8 column (3.5 μm; 4.6 mm I.D. × 150 mm) (X Bridge), isocratic elution with 0.05% TFA in H_2O/0.05% TFA in MeCN (85:15), column temperature 25 °C, 1.0 mL/min, 215 nm, 10 μL injection. Retention times: **6a** (3.2 min), resorcinol **7** (3.4 min), impurity B (4.0 min), impurity C (4.3 min), **1a** (6.0 min), **6b** (8.4 min), impurity A (12.8 min), **1b** (18.7 min).

General Procedure for the Synthesis of 8-Acetamide-3-hydroxy-6*H*-benzo-[*c*]-chromene-6-one (1b). To a mixture of 5-acetamido-2-bromobenzoic acid **6b** (0.775 mmol 1.0 equiv), resorcinol **7** (2.32 mmol, 3.0 equiv) and H_2O (0.640 mL) were added to the bases in Table 3 (2.56 mmol, 3.3 equiv), followed by stirring with heating. After dissolution was confirmed, the copper catalyst (0.232 mmol, 0.3 equiv) was added to this solution, and the mixture was stirred for 1−4 h at 50−100 °C. The slurry was stirred at 0−10 °C for 10 min; 6 M of hydrochloric acid (5 mL) and H_2O (5 mL) were added followed by filtration. The filtered cake was further washed with H_2O (3 mL) and dried in vacuo to afford compound **1b** as a solid.

Manufacturing Synthesis for 8-Acetamide-3-hydroxy-6*H*-benzo-[*c*]-chromene-6-one (1b). To a mixture of H_2O (1300 L), resorcinol **7** (166 kg, 1.51 mol) and 5-acetamide-2-bromobenzoic acid **6b** (130 kg, 0.504 mol) were added 4 M of a NaOH aqueous solution (145 kg, 0.504 mol). After dissolution was confirmed, Na_2CO_3 (123 kg, 1.16 mol) was added to this solution, followed by stirring at 50 °C. CuI (28.8 kg, 0.151 mol) was added to this slurry, and the mixture was stirred for 6 h at 50 °C. When reaction was completed as indicated by HPLC (conv. >98.5%), the reaction mixture was heated to 60 °C, and 4 M of a NaOH aqueous solution (749 kg) and H_2O (2600 L) were added to the reaction solution. After heating and stirring at 60 °C for 1 h, filtering was performed using cellulose powder under pressure for 10 h to remove any insolubles. The reaction mixture was cooled to 30 °C, and acetonitrile (300 kg) and 12 M of hydrochloric acid (458 kg) were added to maintain the internal temperature at less than 30 °C, followed by stirring for 3 h. Thereafter, a precipitated solid was filtered, and the solid was further washed with H_2O (650 L) and dried in vacuo in an oven to a constant weight at 50 °C to afford compound **1b** (103.76 kg, 76.5%) as a pale gray solid. HPLC purity: 93.6 area %. Mp: 340−353 °C decomposed, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H), 6.74 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 8.00 (dd, J = 8.8, 2.4 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.50 (d, J = 2.4 Hz, 1H), 10.25 (s, 1H), 10.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.72, 160.56, 159.22, 151.50, 138.74, 130.08, 126.14, 124.26, 122.50, 119.38, 118.13, 113.13, 109.49, 102.91, 24.06. IR (KBr): cm^{-1} 3339, 3252, 3187, 1717, 1665, 1619, 1600, 1548, 1490, 1458, 1408, 1370, 1312, 1274, 1165, 1129, 1026, 896, 836, 777, 726, 632, 550, 467. HRMS: calcd for $C_{15}H_{11}NO_4$ [M^+]: 269.0688. Found: 269.0687.

Manufacturing Synthesis for 8-Amino-3-hydroxy-6*H*-benzo-[*c*]-chromene-6-one·PTSA (1a·PTSA). A mixture of 8-acetamide-3-hydroxy-6*H*-benzo [*c*] chromene-6-one **1b** (103 kg, 0.383 mol), 4-toluenesulfonic acid monohydrate (218 kg, 1.15 mol), EtOH (1230 kg), and H_2O (206 kg) was heated to 75 °C and stirred for 23.5 h. When the reaction was completed as indicated by HPLC (conv. >99.5%), the reaction mixture was cooled to −10 °C/h over 7 h, resulting in the precipitation of the crude product and held at 0 °C to 10 °C for 4 h. The product was collected by filtration, washed with EtOH (408 kg), and dried in vacuo in an oven to a constant weight at 50 °C to afford compound **1a**·PTSA (118.9 kg, yield 77.8%) as a yellow solid. HPLC purity: 99.95 area %. Mp: 300 °C decomposed, ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.29 (s, 3H), 6.76 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.9, 2.4 Hz, 1H), 6.97 (br s, 3H), 7.11−7.14 (m, 2H), 7.50 (dt, J = 8.0, 1.8 Hz, 2H), 7.57 (dd, J = 8.9, 2.4 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 8.22 (d, J = 8.9 Hz, 1H), 10.24 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.27, 159.71, 151.77, 145.04, 138.14, 135.66, 131.97, 128.27, 128.11, 125.53, 124.64, 123.52, 120.57, 119.95, 113.34, 109.22, 103.03, 20.83. IR (KBr): cm^{-1} 3327, 2927, 2648, 2016, 1737, 1623, 1547, 1495, 1462, 1369, 1325, 1275, 1209, 1174, 1127, 1011, 901, 845, 817, 778, 726, 689, 570, 538, 460. HRMS: calcd for $C_{13}H_9NO_3$ [M^+ − PTSA]: 227.0582. Found: 227.0581.

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Notes

The authors declare no competing financial interest.

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(4) (a) The cost information of regents: CuI USD 40/kg, resorcinol **7** USD 12/kg, K_2CO_3 USD 6/kg, Na_2CO_3 USD 0.5/kg, $Pd_2C1_2(PPh_3)_2$ USD 3300/kg, 10% Pd/C USD 1780/kg, H_2 USD 0.029/L, BBr_3 USD 260/kg, PTSA·H_2O USD 46/kg. The cost information is referred by actual purchase price. (b) Cost information of starting materials **2**, **3**, and **6b** is not disclosable, but bromobenzoic acid **6b** and **3** are about the same prices, and boronic acid **2** is much more expensive than resorcinol **7**.

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(6) 8-Nitro-3-hydroxy-6*H*-benzo [*c*] chromene-6-one **5** via the Hurtley reaction was synthesized in 40% yield, see: (a) Krzeszewski, M.; Vakuliuk, O.; Gryko, D. T. *Eur. J. Org. Chem.* **2013**, *25*, 5631−5644. 8-Amino-3-hydroxy-6*H*-benzo [*c*] chromene-6-one derivatives synthesis via the Hurtley reaction were reported, but not listed isolated yield, see: (b) Sun, W.; Cama, L. D.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1468−1472.

(7) All impurity profile was observed by HPLC assay in the filtrate solution which was filtered off in precipitated solid.

(8) There is no observation of impurities in stirring 60−100 °C for 1−5 h with **6b**, resorcinol **7**, base, and H_2O before adding copper catalyst.

(9) Residual copper was not able to control N-alkylation in next step, see: Ohno, A.; Kudou, K.; Katsuhira, T. WO/2014/098046 A1.

(10) To a suspension of crude **1b** and H_2O (15 v/w), 28% NH_3 aq (5 v/w) was added and stirred for 3 h. Addition of EtOH (3 v/w) and filtered. The filtered cake was further washed with 2 M HCl (5 v/w) and H_2O (5 v/w) and dried in vacuo to afford **1b** as a solid (78%, <50 ppm Cu).

(11) Compound **8** was assumed by ^{1}H NMR in the dryness of filtered solvent of **1b** solution and mass spectrometry in the filtered solution. ^{1}H NMR (500 MHz, D_2O) δ: 2.19 (s, 3H), 6.16−6.18 (m, 2H), 6.91 (d, J = 8.9 Hz, 1H), 7.34 (dd, J = 8.2 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.44 (dd, J = 8.2, 2.1 Hz, 1H); MS (ESI): m/z 286 [M − H]$^-$.

(12) Although qualitative analysis was not studied in copper salt, the salt color changed to red from light gray white and confirmed a decrease in weight.

(13) KC FROCK that produced by Nippon Paper Industries, Co., Ltd. is available.

(14) Preparation of solubility determination sample: Sampling by syringe from the suspension and filtered by filter (0.45 μm). To pipet (1000 μL) immediately, addition of 1 M HCl (2000 μL) and mess up to 50 mL by MeCN/H_2O (2:1).

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