Process Development of a Novel Anti-Inflammatory Agent. The Regiospecific Bromination of 4′-Acetylmethanesulfonanilide

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Abstract:

An efficient, practical synthesis of a novel antiinflammatory agent (FK3311, 1) which is acceptable environmentally and could be used for pilot plant manufacture is described. Regiospecific bromination of 4′-acetylmethanesulfonanilide, allowing selective side chain or nuclear halogenation, also has been investigated. Development efforts focused on the optimized Ullmann coupling reaction conditions and the isolation and purification of 1 to give satisfactory quality product (99.8% purity) according to the new and concise synthetic route.

Introduction

Classical non-steroidal anti-inflammatory drugs (NSAIDs) represented by indomethacin and aspirin have been extremely useful for the treatment of rheumatoid arthritis (RA). However, the adverse effects of NSAIDs, such as gastrointestinal irritation, are well-known.[1] The recent discovery of a new class of drugs, illustrated by nimesulide[2] and flosulide,[3] which have potent anti-inflammatory effects without causing gastrointestinal irritation has been attributed to selective inhibition of COX-II (cyclooxygenase-2), with no effect on COX-I (cyclooxygenase-1), the latter enzyme considered responsible for the side effects with the earlier drugs (Figure 1). This discovery has prompted a large effort to find novel, selective inhibitors of COX-II.[4,5]

During the course of our investigations into COX-II selective inhibitors, 4′-acetyl-2′-(2,4-difluorophenoxy)methanesulfonanilide (FK3311, **1**), with very potent and selective activity, was discovered.[6] For complete biological evaluation, we required large quantities of compound **1** for *in vitro* and *in vivo* studies of efficacy and pharmacokinetics.

Tsuji and co-workers prepared **1** *via* the synthetic route illustrated in Scheme 1 (route A).[6] This method was effective for small-scale preparations; however, from the point of view of industrial-scale synthesis, there are several severe disadvantages. For example, the NOx gas evolved at the nitration step in the Sandmeyer reaction produces major environmental problems. In addition, oxidation and reduc-
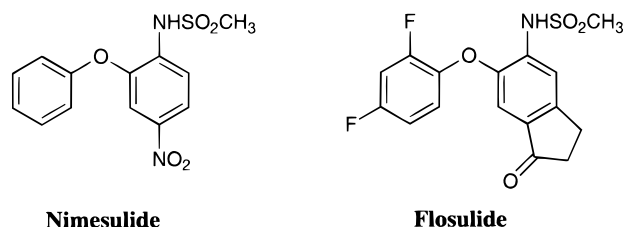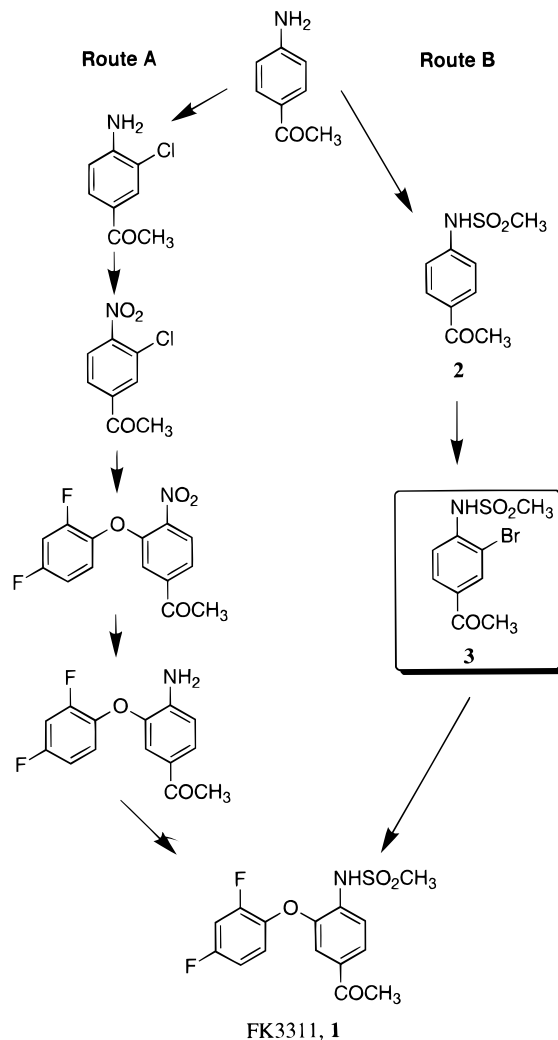

Figure 1. Structures of COX-II inhibitors.

Scheme 1. Routes to 1 from 4-aminoacetophenone

FK3311, **1**

tion in one process causes a prolonged and, additionally, conceptually inefficient procedure. In order to develop a more inexpensive, direct, and practical synthesis of **1**, we investigated the new, concise synthetic method illustrated

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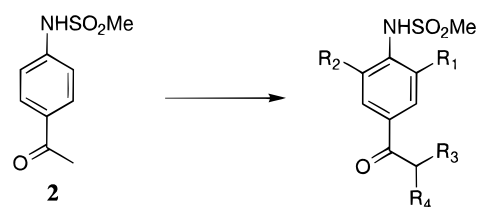
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Table 1. Regiospecific bromination of **2**

	R$_1$	R$_2$	R$_3$	R$_4$
3	Br	H	H	H
4	H	H	Br	H
5	Br	Br	H	H
6	Br	H	Br	H
7	H	H	Br	Br
8	Br	H	Br	Br

							product ratio[a]						
entry	solvent	equiv of AcONa	meth	equiv of Br$_2$	temp (°C)	time (min)	2	3	4	5	6	7	8
1	AcOH	0	A	1.0	15	360	30	0	58	0	5	7	0
2	AcOH	0	A	2.0	15	360	0	0	19	0	8	21	50
3	AcOH	0	A	1.0	55	60	9	0	85	0	0	6	0
4	AcOH	0	A	2.0	55	120	0	0	17	0	0	83	0
5	AcOH−H$_2$O	0	B	1.0	15	360	27	73	0	0	0	0	0
6	AcOH−H$_2$O	0	B	2.0	5	360	3	97	0	0	0	0	0
7	AcOH−H$_2$O	0	B	2.0	15	360	2	97	1	0	0	0	0
8	AcOH−H$_2$O	0	B	1.0	55	60	20	59	7	0	14	0	0
9	AcOH−H$_2$O	0	B	2.0	55	60	0	65	0	11	24	0	0
10	AcOH−H$_2$O	5	C	1.0	15	120	3	95	0	1	0	0	0
11	AcOH−H$_2$O	5	C	1.05	15	120	1	98	0	1	0	0	0
12	AcOH−H$_2$O	5	C	2.0	15	120	0	49	0	51	0	0	0
13	AcOH−H$_2$O	5	C	1.0	55	60	6	89	0	5	0	0	0
14	AcOH−H$_2$O	5	C	2.0	55	60	0	34	0	66	0	0	0

[a] The product ratio was determined by HPLC (YMC GEL ODS 120 Å s-7, 35% CH$_3$CN in water pH = 6.0, 254 nm, 1 mL/min).

Scheme 2. Preparative route to **2**
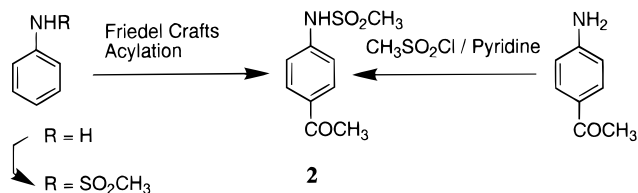
in Scheme 1 (route B). Our plan called for the coupling of 4′-acetyl-2′-bromomethanesulfonanilide (**3**) with 2,4-difluorophenol to produce **1** directly.

Results and Discussion

Amide **2**, the key intermediate for **3**, can be obtained by two independent methods (Scheme 2). The first method involves Friedel−Crafts acylation of commercially available sulfonanilide.[7] However, the requirement for AlCl$_3$ makes this procedure extremely tedious for large-scale preparations. In an alternate route, the commercially available and inexpensive 4-aminoacetophenone serves as the starting material. Sulfonylation of 4-aminoacetophenone with methanesulfonyl chloride has been shown to provide **2** in good yield.[8] Adaptation to a large scale provided the requisite starting material **2** as a solid in 96% yield. As part of efforts to develop an inexpensive preparation of **3** amenable to large scale, regiospecific bromination (either of the acetyl group or of the aromatic ring) with the same reagent (bromine) and in the same solvent (acetic acid) was examined. Herein

we report the results of these endeavors and the remarkable observation that, simply by changing reaction conditions, complete regiospecificity can be obtained.

Although several systems[7,9] are known for the bromination of acetyl sulfonanilides, these methods furnished only the corresponding acetyl brominated compounds; in no instance was aromatic bromination observed. Indeed, to our knowledge, **3** has not been described previously in the literature. On the other hand, Rosenmund[10] reported a procedure for regioselective bromination of hydroxy or methoxy acetophenone derivatives in which the ortho position was activated. This discovery prompted us to investigate simple bromination of **2** to provide the key intermediate **3**.

We selected bromine as an inexpensive and readily available reagent in glacial acetic acid as solvent for large-scale preparations. In our initial experiments, we were disappointed to find that no 4′-acetyl-2′-bromomethanesulfonanilide was obtained at all but only 4′-(2-bromoacetyl-)methanesulfonanilide along with traces of polybrominated derivatives **6**−**8**. As shown in Table 1, with acetic acid as solvent only side chain bromination proceeded at higher temperatures (55 °C) (entries 3, 5). Concerning the mechanism of bromination of the acetyl group, it is not totally clear, but the undesirable side chain reaction is presumed to proceed by acid-catalyzed enolization of the ketone and subsequent electrophilic attack on the enol by bromine.

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Table 2. Regiospecific bromination of 3 and 4
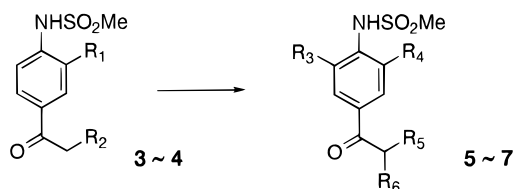
entry	R_1	R_2	starting material	meth[a]	equiv of Br$_2$	temp (°C)	time (min)	R_3	R_4	R_5	R_6	product	yield (%)[b,c]
1	Br	H	3	A	1.0	55	10	H	Br	Br	H	6	100
2	Br	H	3	C	1.0	55	360	Br	Br	H	H	5	45 (43)
3	Br	H	3	C	2.0	60	120	Br	Br	H	H	5	57[d]
4	H	Br	4	A	1.0	55	180	H	H	Br	Br	7	97
5	H	Br	4	C	1.0	55	10	H	Br	Br	H	6	40 (20)[e]

[a] Method A: in AcOH. Method C: AcONa (5 equiv) in AcOH−water. [b] Yields were determined from isolated yields and ^{1}H NMR analysis of crude products. [c] Yields in parentheses refer to percent of recovered starting material. [d] Crude product was purified by trituration with 2-PrOH. [e] 16% of 7 was included in the product.
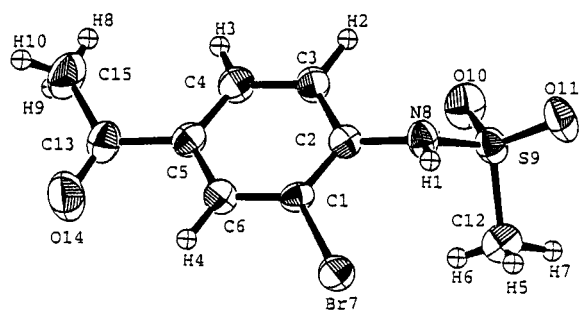
Figure 2. ORTEP drawing (41% ellipsoids) of 3 with crystallographic numbering scheme. Selected bond lengths (Å): Br(7)−C(1) = 1.895(4), S(9)−O(11) = 1.433(3), S(9)−C(12) = 1.754(6), N(8)−C(2) = 1.402(5), C(1)−C(6) = 1.372(5), C(3)−C(4) = 1.370(6), C(5)−C(6) = 1.407(6), C(13)−C(15) = 1.507(7), S(9)−O(10) = 1.433(3), S(9)−N(8) = 1.641(4), O(14)−C(13) = 1.203(5), C(1)−C(2) = 1.396(5), C(2)−C(3) = 1.400(6), C(4)−C(5) = 1.378(6), C(5)−C(13) = 1.498(6).

However, Larsen[11] reported side chain bromination of 4′-acetylmethanesulfonanilide using bromine and benzoyl peroxide in chloroform. Thus, side chain reaction possibly occurs readily at high temperatures by a radical mechanism.

In order to prevent side chain bromination, we investigated the possibility of aromatic bromination in greater detail. In the course of our research, addition of water proved to be useful to prevent side chain bromination and promote aromatic bromination whilst also preventing freezing of the reaction mixture. Thus we further searched for optimized reaction conditions and found that only aromatic bromination and no side chain bromination could be detected under cooled conditions (<5 °C) (entry 6). Under these conditions with an excess of bromine, complete aromatic bromination occurred with no undesired products, leading to 97% of 3 (Figure 2).[12]

In spite of these excellent results, excess use of bromine was not desirable for a large-scale preparation. Excess use

of materials is not compatible with inexpensive preparation, and in addition, it is necessary to perform an extraneous procedure such as deactivation of the residual bromine in order to prevent undesired reactions. We therefore investigated more efficient systems and found that the removal of hydrogen bromide by sodium acetate enhances the reactivity in the bromination and was useful for the prevention of acid-catalyzed enolization, presumably by a buffering effect. Indeed, in the presence of added sodium acetate, no side chain bromination occurred even at a higher temperature (55 °C) (entries 13, 14) and reaction was complete in only 2 h with only 1.05 equiv of bromine under cooled conditions (<15 °C) (entry 11), whilst 6 h was required under the previous conditions for complete reaction with 2 equiv of bromine. We thus prepared 52.5 kg of 3 suitable for the preparation of 21.7 kg of 1.

Following these observations, we wondered whether the use of these conditions would lead to dibromo compounds efficiently (Table 2). 4′-(2,2-Dibromoacetyl)methanesulfonanilide was quantitatively prepared by bromination of 4′-(2-bromoacetyl)methanesulfonanilide in acetic acid at high temperature (55 °C, entry 4). 4′-(2-Bromoacetyl)-2′-bromomethanesulfonanilide also could be quantitatively prepared from 4′-acetyl-2′-bromomethanesulfonanilide (entry 1); aromatic bromination was somewhat difficult. Aromatic bromination of 4′-acetyl-2′-bromomethanesulfonanilide at 55 °C for 6 h in acetic acid and water with 5 equiv of sodium acetate was successful; however, conversion was not so good, with an approximately 1:1 mixture of starting material and 5 being obtained (entry 2). Higher temperature conditions were not successful either, but no side chain brominated compounds could be detected. An analytical sample of 4′-acetyl-2′,6′-dibromomethanesulfonanilide was obtained by the reaction of excess bromine with 4′-acetyl-2′-bromomethanesulfonanilide at a higher temperature (60 °C, entry 3) and successive crystallization and washing with 2-propanol. In the case of 4′-(2-bromoacetyl)methanesulfonanilide, aromatic bromination was not successful (55 °C, entry 5) compared the reaction of the monobrominated compound with an acetyl group. The same compound was rather easily

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Table 3. Ullmann coupling reaction of 3 with 2,4-difluorophenol (1.2 mol/mol)

entry	solvent	base (mol/mol)	equiv of CuCl[a]	temp (°C)	time (min)	product ratio[b] 1	2	3
1	DMF	K_2CO_3 (1.2)	1.5	130	120	0	0	100
2	quinoline	K_2CO_3 (1.2)	1.5	170	300	<5	0	>95
3	2-picoline	K_2CO_3 (1.2)	1.5	130	150	<5	0	>95
4	pyridine	K_2CO_3 (1.2)	1.5	115	300	54	35	11
5	pyridine	$NaHCO_3$ (2.4)	1.5	115	360	25	10	65
6	pyridine	$KHCO_3$ (2.4)	1.5	115	360	7	6	87
7	pyridine	NaOH (1.2)	1.5	115	360	11	3	86
8	pyridine	KOH (1.2)	1.5	115	360	11	0	89
9	pyridine	K_2CO_3 (1.2)	0.12	115	360	25	1	74
10	pyridine	K_2CO_3 (1.2)	0.5	115	360	45	10	45
11	pyridine	K_2CO_3 (1.2)	0.75	115	360	55	14	31
12	pyridine	K_2CO_3 (1.2)	1.5	115	360	54	35	11
13	pyridine	K_2CO_3 (1.2)	0.75	115	360	55	14	31
14	pyridine	K_2CO_3 (1.2)	0.75	115	540	53	14	33
15	pyridine	K_2CO_3 (2.4)	0.75	115	360	58	15	27
16	pyridine	K_2CO_3 (4.8)	0.75	115	420	50	24	29

[a] Catalyst. [b] The product ratio was determined by HPLC (YMC GEL ODS 120 Å S-7, 50% CH_3CN in water pH = 7.6, 254 nm, 1 mL/min).

Scheme 3. Ullmann coupling reaction
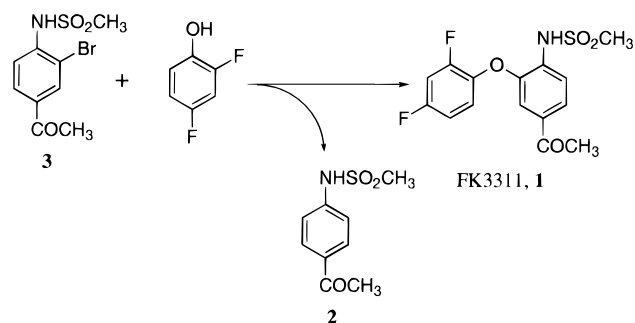
prepared in good yield by the side chain bromination of 4′-acetyl-2′-bromomethanesulfonanilide according to method A (entry 1).

Whilst the source of the unusual regiospecific bromination of **2** is not clear at this point, our best speculation is that, in the presence of water or sodium acetate, N-bromination of the methanesulfonamide group occurs, followed by an intramolecular delivery of Br to the ortho position. Otherwise, acid-catalyzed generation of the enol species leads to selective trapping of reagent at the more electron rich carbon atom. Control experiments indicated that **3** or **4** did not undergo any bromine migration processes when exposed to the various reaction conditions employed in this work.

With an efficient preparation of key bromide **3** in hand and the compound available in large quantities, the Ullmann coupling with 2,4-difluorophenol was intensively investigated (Scheme 3). Ullmann coupling reactions have been demonstrated to be efficient methods for preparing diphenyl ethers. The most general approach involves the reaction of alkali metal phenolate with a halobenzene in the presence of a catalyst such as copper or a copper salt.[13] However, this reaction usually has severe disadvantages when applied to an industrial synthesis. For example, high-temperature conditions (typically 130−220 °C)[14,15] and long reaction

times (14 h to 6 days)[16,17] are usually required unless there are strongly electron withdrawing groups on the halobenzene moiety.[18] Furthermore, reactions of compounds which have acidic groups such as sulfonanilides with phenols are not well-known. In 1964, Bacon[19,20] showed that pyridine and quinoline were useful for carrying out the Ullmann coupling reaction of nonactivated aryl halides with phenols. Weingarten[21] also reported that copper(I) halides were better catalysts than copper metal or copper oxide. During our numerous studies as shown in Table 3, **3** could be coupled with 2,4-difluorophenol only in the case where copper(I) chloride and fine granulated potassium carbonate (<10 μm) were used in pyridine as solvent. To our surprise, reactions under higher temperature conditions in quinoline or 2-picoline hardly proceeded at all (entries 2, 3). Therefore, we focused on optimizing reaction conditions in this system to give high yields and fewer impurities and to make workup possible for an industrial scale.

In the presence of a catalytic amount of copper(I) chloride, the reaction proceeded sluggishly (entry 9). On the other hand, debrominated product **2** was produced in large quantities in the presence of excess copper(I) chloride under the same conditions (entry 12). We also investigated the amount of fine granulated potassium carbonate. Whilst the use of excess fine granulated potassium carbonate slightly improved the yield (entry 15), a very large excess increased the viscosity of the reaction mixture, and reaction failed to proceed smoothly. Optimized reaction conditions (entry 15) could be established in this way, but we were disappointed to find that the yield was not satisfactory from the point of

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Table 4. Ullmann coupling reaction of **3** with 2,4-difluorophenol[a]

entry	4	yield (%)[b]
1	1.2	46
2	2.0	59
3	1.2	57[c]

[a] In all cases, the base was K_2CO_3 (2.4 mol/mol), the catalyst was CuCl (0.75 equiv), the temperature was 115 °C, and the duration of the reaction was 360 min. [b] The yield was determined by quantitative HPLC. [c] The reaction was carried out with anhydrous conditions being maintained with $MgSO_4$.

Table 5. Selective isolation of the sodium salt of **1** in the presence of excess NaOH

entry	equiv of NaOH	temp (°C)	content ratio of **1**[a]		
			org layer	aq layer	ppt
1	1.0	25	14	86	0
2	1.05	25	1	99	0
3	5.0	25	13	0	87
4	8.0	25	8	0	92
5	8.0	5	4	0	96

[a] Ratio determined by quantitative HPLC.

view of an inexpensive and practical synthesis, which was required in an industrial synthesis.

As shown in Table 4, one of the efficient methods to enhance the yield was to use excess 2,4-difluorophenol, but excess use of this expensive agent was not recommended for inexpensive preparation. Another way to improve the yield was to perform the reaction under anhydrous conditions. Although the mechanism of the Ullmann coupling reaction in basic solvents is unknown, Gerard[22] pointed out that these solvents complex with copper salts and hence solubilize them, allowing the interaction of copper salts with aryl halides. We suspected that water lowered the activity of this complex, and we investigated the reaction in the presence of dehydrating agents such as 4A molecular sieves or magnesium sulfate under a nitrogen atmosphere. It was found that a significant improvement in the yield was achieved. In order to have this principle applied to the large-scale synthesis, we carried out the reaction under a nitrogen atmosphere continuously distilling water with pyridine and adding fresh pyridine at the same rate.

In spite of the established and optimized reaction conditions, the isolation of the desired product was enormously difficult on a large scale. Indeed, the similar properties of **1**−**3** prevented efficient separation by the usual methods (recrystallization and even chromatography). During our continuous efforts, it was found that the sodium salt of **1** only precipitated in the presence of excess sodium hydroxide. This phenomenon was attributed to the higher hydrophobic property of the sodium salt of **1**, compared with **2** or **3**. This discovery prompted us to find conditions under which the sodium salt of **1** was quantitatively obtained by salting-out techniques (Table 5).

By using the described reaction conditions and isolation methods, we could prepare **1** as dark-yellow crystals of good

(22) Gerard, S. *J. Org. Chem* **1985**, *50*, 3717.

purity (98% by HPLC). However, in general, compounds used as pharmaceutical agents have to be of extremely high chemical purity and free from toxic or colored impurities. This is usually achieved by recrystallization under highly clean conditions. **1** required special treatment because the Ullmann reaction was at the final stage and inevitably traces of cuprous residues and methylene chloride as extraction solvent remained. For complete removal of cuprous residues and decreasing colored impurities, treatment with a short column of alumina (AC-12), followed by activated carbon, was introduced. Purified and absolutely white **1** which has satisfactory quality was obtained by recrystallization from ethanol. We have prepared **1** on a scale of 45 kg using this procedure.

Conclusions

In this paper we have described a concise and efficient synthesis of the COX-II selective anti-inflammatory agent **1**. Remarkable effects in the bromination of 4′-acetyl-methanesulfonanilide and related monobrominated analogs were observed, allowing completely regioselective nuclear or side chain bromination simply by control of the reaction conditions. These observations enhance the versatility of bromine as an inexpensive, readily available starting material, suitable for industrial-scale synthesis and as an activating group for a variety of C−C and C−heteroatom bond forming processes. Process improvements and optimization for coupling of key bromide **3** with 2,4-difluorophenol resulted in an inexpensive, direct, and practical synthesis of **1**. These described methods are extremely useful for preparing **1** on a large scale.

Experimental Section

General Procedures. 4-Aminoacetophenone of pure grade was commercially available from the EMS-DOT-TIKON AG. γ-Alumina (AC-12) was commercially available from Sumitomo Chemical Co. Ltd. All other chemicals were obtained from the usual commercial suppliers. We employed a modified literature procedure for the preparation of 4′-acetylmethanesulfonanilide.[7] Melting points were measured on a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a HITACHI IR-260-10 spectrometer. NMR spectra were measured on a Brucker AC200P (^{1}H, 200 MHz). Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. Reagents and solvents were used as obtained from commercial suppliers without further purification.

Large-Scale Preparation of 4′-Acetylmethanesulfonanilide (2). Methanesulfonyl chloride (26.5 kg, 231 mol) was added dropwise over 30 min to a solution of 4-aminoacetophenone (25.0 kg, 185 mol) and N-methylmorpholine (23.4 kg, 231 mol) in methylene chloride (250 L) with stirring at 20−25 °C, and the resulting mixture was stirred at ambient temperature for 1 h. Separately, an aqueous

solution was prepared by dissolving sodium hydroxide (37.0 kg, 925 mol) in water (250 L). The reaction mixture obtained above was added dropwise to this aqueous solution with stirring at 25−30 °C. After completion of the addition, the resulting mixture was further stirred at ambient temperature for 15 min, the aqueous layer was separated, and the organic layer was re-extracted by water (25 L). The aqueous layers were combined, and to this solution were added ethyl acetate (625 L), acetone (125 L), and 35% hydrochloric acid in water (37.5 L) with stirring at 18−25 °C. The layers were separated, and the aqueous layer was re-extracted with ethyl acetate (150 L). The combined organic layer was washed with saturated sodium hydrogen carbonate in water (50 L), concentrated to ~125 L under reduced pressure, treated with 2-propanol (125 L), and again concentrated to 125 L under ambient conditions. To the residue was added water (375 L), the mixture was cooled to 5 °C, and the precipitate was filtered off, washed with water (50 L), and dried under reduced pressure to afford **2** (38.0 kg, 96% yield) as a yellowish solid: mp 155−156 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.55 (s, 3H), 3.15 (s, 3H), 7.29 (dd, 2H, J = 6.9, 2.6 Hz), 7.94 (dd, 2H, J = 6.8, 1.9 Hz), 10.4 (br s, 1H); IR (Nujol) 1670, 1600 cm^{-1}; MS (EI) m/z 214 (M$^+$). Anal. Calcd for C$_9$H$_{11}$NO$_3$S: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.31; H, 5.01; N, 6.52.

Large-Scale Preparation of 4′-Acetyl-2′-bromomethane-sulfonanilide (3) (Method B). Bromine (59.0 kg, 370 mol) was added dropwise over 1 h to a solution of 4′-acetyl-methanesulfonanilide (**2**) (39.4 kg, 185 mol) in glacial acetic acid (788 L) and water (263 L) with stirring at 15 °C. After completion of the addition, the resulting mixture was further stirred at the same temperature for 6 h, was treated with sodium bisulfite (23.1 kg, 222 mol) in water (115 L), and then was concentrated under reduced pressure to ~120 L. To the residue was added water (400 L), and stirring was continued at 5 °C overnight. The precipitate was filtered off and washed with water (160 L). Drying under reduced pressure afforded 4′-acetyl-2′-bromomethanesulfonanilide (**3**) (52.5 kg, 97% yield) as a white solid: mp 123−125 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.58 (s, 3H), 3.17 (s, 3H), 7.60 (d, 1H, J = 8.5 Hz), 7.95 (dd, 1H, J = 8.5, 2.0 Hz), 8.18 (d, 1H, J = 2.0 Hz), 9.60 (br s, 1H); IR (Nujol) 1690, 1600 cm^{-1}; MS (EI) m/z 292 (M$^+$), 294 (M$^+$ + 2). Anal. Calcd for C$_9$H$_{10}$BrNO$_3$S: C, 37.00; H, 3.45; N, 4.79. Found: C, 36.82; H, 3.25; N, 4.71.

X-ray Crystallographic Analysis[12] of 3. Colorless prismatic crystals of **3** (C$_9$H$_{10}$BrNO$_3$S) were grown from acetone−isopropyl ether solution. Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite-monochromatized Cu Kα radiation (λ = 1.541 78 Å). Crystal data: C$_9$H$_{10}$BrNO$_3$S, M_r = 292.15, triclinic, a = 8.969(7) Å, b = 11.00(3) Å, c = 5.590(5) Å, β = 94.96(7)°, V = 543(1) Å^3, Z = 2, D_{calc} = 1.786 g/cm^3, μ = 68.78 cm^{-1}, $F(000)$ = 292.00, T = 297 K. A total of 1890 reflections were collected using the ω−2θ scan technique within a 2θ range of 125.7°. The structure was solved by heavy-atom Patterson methods and refined by a full-matrix least-squares method using 1852 reflections (I > 1.50$\sigma(I)$).

The final refinement converged to R = 0.036 and R_w = 0.038.

Large-Scale Preparation of 4′-Acetyl-2′-bromomethane-sulfonanilide (3) (Method C). Bromine (31.0 kg, 194 mol) was added dropwise over 1 h to a solution of 4′-acetyl-methanesulfonanilide (**2**) (39.4 kg, 185 mol) and sodium acetate (75.8 kg, 924 mol) in glacial acetic acid (788 L) and water (263 L) with stirring at 15 °C. After completion of the addition, the resulting mixture was further stirred at the same temperature for 2 h and was then concentrated under reduced pressure to ~260 L. To the residue was added water (591 L), and stirring was continued at 5 °C overnight. The precipitate was filtered off and washed with water (150 L). Drying under reduced pressure afforded 4′-acetyl-2′-bro-momethanesulfonanilide (**3**) (52.4 kg, 97% yield) as a white solid, identical with the material obtained in the preceding experiment (^{1}H NMR, TLC).

4′-(2-Bromoacetyl)methanesulfonanilide (4) (Method A). Bromine (15.0 g, 94 mmol) was added dropwise over 5 min to a solution of 4′-acetylmethanesulfonanilide (**2**) (20 g, 94 mmol) in glacial acetic acid (400 mL) with stirring at 55 °C. After completion of the addition, the resulting mixture was further stirred at the same temperature for 10 min and became colorless. Removal of acetic acid and trituration with 2-propanol (200 mL) afforded 4′-(2-bro-moacetyl)methanesulfonanilide (**4**) (25.12 g, 92% yield) as a white solid: mp 167−168 °C dec; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.14 (s, 3H), 4.85 (s, 2H), 7.30 (d, 2H, J = 8.7 Hz), 7.99 (d, 2H, J = 8.7 Hz), 10.46 (br s, 1H); IR (Nujol) 1695, 1670, 1610, 1595, 1520 cm^{-1}; MS (EI) m/z 292 (M$^+$), 294 (M$^+$ + 2). Anal. Calcd for C$_9$H$_{10}$BrNO$_3$S: C, 37.00; H, 3.45; N, 4.79. Found: C, 37.14; H, 3.31; N, 4.70.

4′-Acetyl-2′,6′-dibromomethanesulfonanilide (5) (Method C). 4′-Acetyl-2′,6′-dibromomethanesulfonanilide (**5**) was prepared by the reaction of 4′-acetyl-2′-bromomethanesulfo-nanilide (**3**) (2.0 g, 6.8 mmol) and sodium acetate (2.81 g, 34.3 mmol) with excess bromine (2.18 g, 13.6 mmol) in acetic acid−water at a higher temperature (60 °C). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 5 °C. The precipitate was filtered off, washed with water and 2-propanol, and dried *in vacuo* to afford pure 4′-acetyl-2′,6′-dibromomethanesulfonanilide (**5**) as a white solid in 57% yield: mp 164−166 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.61 (s, 3H), 8.19 (s, 2H), 9.85 (br s, 1H); IR (Nujol) 1685, 1590, 1610, 1550 cm^{-1}; MS (EI) m/z 370 (M$^+$), 372 (M$^+$ + 2), 374 (M$^+$ + 4). Anal. Calcd for C$_9$H$_9$Br$_2$NO$_3$S: C, 29.13; H, 2.44; N, 3.77. Found: C, 28.85; H, 2.25; N, 3.65.

4′-(2-Bromoacetyl)-2′-bromomethanesulfonanilide (6). 4′-(2-Bromoacetyl)-2′-bromomethanesulfonanilide (**6**) was prepared from 4′-acetyl-2′-bromomethanesulfonanilide (**3**) (100%, method A): mp 142−145 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.22 (s, 3H), 4.94 (s, 2H), 7.61 (d, 1H, J = 5.2 Hz), 8.00 (dd, 1H, J = 6.0, 2.2 Hz), 7.26 (d, 1H, J = 2.0 Hz), 9.65 (br s, 1H); IR (Nujol) 1680, 1600, 1560, 1500 cm^{-1}; MS (EI) m/z 370 (M$^+$), 372 (M$^+$ + 2), 374 (M$^+$ +

4). Anal. Calcd for $C_9H_9Br_2NO_3S$: C, 29.13; H, 2.44; N, 3.77. Found: C, 28.88; H, 2.28; N, 3.69.

4′-(2,2-Dibromoacetyl)methanesulfonanilide (7). 4′-(2,2-Dibromoacetyl)methanesulfonanilide (**7**) was prepared from 4′-(2-bromoacetyl)methanesulfonanilide (**4**) (97%, method A): mp 190−191 °C dec; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.18 (s, 3H), 7.32 (d, 2H, J = 8.9 Hz), 7.80 (s, 1H), 8.07 (d, 2H, J = 8.8 Hz), 10.58 (br s, 1H); IR (Nujol) 1695, 1605, 1580, 1520 cm^{-1}; MS (EI) m/z 370 (M$^+$), 372 (M$^+$ + 2), 374 (M$^+$ + 4). Anal. Calcd for $C_9H_9Br_2NO_3S$: C, 29.13; H, 2.44; N, 3.77. Found: C, 29.45; H, 2.31; N, 3.75.

4′-Acetyl-2′-(2,4-difluorophenoxy)methanesulfonanilide (1). A mixture of 4′-acetyl-2′-bromomethanesulfonanilide (45 kg, 154 mol), cuprous chloride (11.4 kg, 115 mol), and fine granulated potassium carbonate (54.0 kg, 369 mol) in pyridine (112.5 L) was heated to 115 °C under a nitrogen atmosphere. To this reaction mixture was added dropwise 2,4-difluorophenol (24.0 kg, 184 mol), over 10 min at the same temperature. The reaction was continued for 7 h, pyridine being removed by distillation at the rate of 9 L/h. After cooling, the reaction mixture was added to water (150 L), methylene chloride (360 L), and 35% hydrochloric acid in water (300 L). The organic layer was separated, and the aqueous layer was re-extracted with methylene chloride (90 L, 45 L, 45 L). The organic layers were combined and purified by column chromatography on γ-alumina (AC-12, 180 kg) with additional methylene chloride (360 L). The effluent was reduced to 225 L under reduced pressure. In another vessel, sodium hydroxide (12.3 kg, 308 mol) was dissolved in water (450 L), and this solution was added dropwise to the previous solution at 25 °C. After additional stirring for 15 min, extraction was completed, and 24% sodium hydroxide in water and the purified sodium salt of **1** (45 g) were added. After the precipitation of the sodium salt of **1** at 25 °C, stirring was continued at 5 °C overnight. The precipitated sodium salt of **1** was filtered off and washed with methylene chloride (90 L). In the extraction vessel, methylene chloride (270 L) and water (270 L) were added,

and to this mixture was added the isolated sodium salt of **1** at 25 °C. The extraction mixture was adjusted to pH = 1.0−1.5 with 35% hydrochloric acid (∼12 L). The organic layer was separated and washed with saturated sodium bicarbonate in water (135 L). The organic layer was added to a solution of potassium hydroxide (13.5 kg, 241 mol) in water (270 L) at 25 °C (the potassium salt of **1** never precipitates under these conditions). The aqueous layer was separated, and the organic layer was re-extracted with 5% potassium hydroxide in water (45 L). The combined aqueous layer was treated with activated carbon (4.5 kg). To this filtrate was added 2-propanol (360 L), and the solution was adjusted to pH = 6.0 by 35% hydrochloric acid (∼20 L) at 25 °C. After stirring for 30 min at the same temperature, water (360 L) was added and the solution was cooled to 3 °C. Stirring was continued at the same temperature overnight, and the precipitate was filtered off, washed with water (90 L), and dried under reduced pressure to afford crude **1** (26.8 kg, 51% yield). The crude **1** (23.0 kg, 67.4 mol) was recrystallized from ethanol (138 L) to afford purified 4′-acetyl-2′-(2,4-difluorophenoxy)methanesulfonanilide (**1**) (21.7 kg, 95% yield) as a white solid: mp 117−118 °C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.50 (s, 3H), 3.18 (s, 3H), 3.18 (s, 3H), 7.16−7.83 (m, 3H), 9.49 (br s, 1H); IR (Nujol) 1685, 1605, 1590, 1510 cm^{-1}; MS (EI) m/z 341 (M$^+$). Anal. Calcd for $C_{15}H_{13}F_2NO_4S$: C, 52.78; H, 3.84; N, 4.10. Found: C, 52.49; H, 3.67; N, 4.04.