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First Total Synthesis of Pestasulfamides A and B Through Iminoketene Dimerization of Anthranilic Acid in One-Pot Manner

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Articles

First Total Synthesis of Pestasulfamides A and B Through Iminoketene Dimerization of Anthranilic Acid in One-Pot Manner

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Abstract

Pestasulfamides A and B are phenylbenzene-sulfonamides with an eight-membered dilactam, produced by mangrove endophytic fungus *Pestalotiopsis sp*. HNY36-1D. Herin, the first total synthesis of pestasulfamides A and B was achieved through one-pot protocol. The key step features an iminoketene dimeriazation of anthranilic acid triggered by a sulfonylation in a pyridine/THF system.

Keywords: total synthesis; natural products; phenylbenzene sulfonamides; dibenzodiazocin-2,6-dione

1. Introduction

Primary sulfonamides are known as privilegged drug pharmacophore and widely used as drugs [1–4]. With superior physical property, metabolic stability, and easiness to synthesis, primary and secondary sulfonamides have been attracted much attension from synthetic and medicinal chemists. Among the sulfonamide family, a tertiary sulfonamide have not been pushed to the forefront of the drug design probaly due to lackness of acidic hydrogen atom at the nitrogen, which can act as hydrogen bonding donar. Unlike that trend, recent studies revealed that some tertiary sulfonamides can play a novel pharmacophore probably due to their good binding properties against target enzymes and/or receptors such as liver X receptor antagonists (LXRs) [5], butylcholinesterase inhibitors for the treatment of Alzheimer's disease [6], antiproliferative activities [7], and a-carbonic anhydrase of *Helicobacter pylori* (HpaCA) inhibitors [8]. On the other hands, natural products containing sulfonamide units are relatively rare, although drug-like compounds containing sulfonamides are well-developed [9].

In this context, phenylbenzenesulfonyl amide-type natural product, pestasulfamides A (**1**) and B (**2**), were isolated in 2023 from mangrove endophytic fungus *Pestalotiopsis sp*. HNY36-1D by the Sun and She group (Figure 1) [10]. The structures of **1** and **2** were determined by 1D and 2D NMR, HR-ESIMS, IR, as well as a single crystal X-ray diffraction for **2**. Structurally, pestasulfamides A (**1**) and B (**2**) are rare dibenzodiazocines that differ in their number of phenylbenzenesulfonyl amide group. In bioassay, pestasulfamide A (**1**) eihibitted potent anti-acetylcholine esterase (AChE) activities with IC50 value 11.94 mM, while pestasulfamides B (**2**) did not show the AChE inhibitory activity. Authors conclude that the origin of AChE inhibitory activity come from the closed loop of cyclic dibenzodiazocines, which caused by hydrogen bonding of nitrogen atom of **1**. In this isolation report, known sargassulfamide A (**3**) were also isolated as acyclic analogue with two cyclic analogues **1** and **2**, which suggests that sargassulfamide A (**3**) or known phenylbenzenesulfonyl amide natural product (**4**) may be bioprecursor of pestasulfamides A (**1**) and B (**2**) through stepwise amidation/cyclization [11,12]. Among sulfonamide natural products [13,14], phenylbenzenesulfonyl amides are quite rare [15,16].

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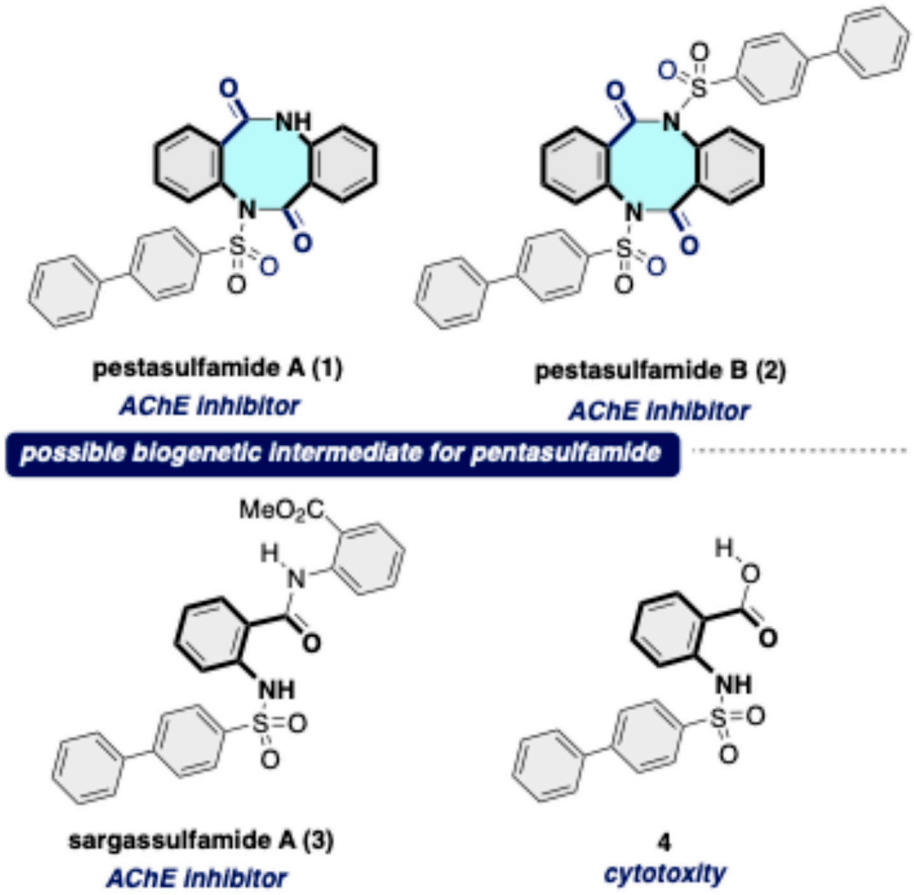

Figure 1. Structures of phenylbenzenesulfonyl-substituted natural products.

Dibenzodiazocin-2,6-diones have drawn attention from the organic chemists due to their cyclic diamide flexible eight-membered structure [17], intriguing planner chirality [18–20], and chemosensitivities [21]. Traditionally, dibenzodiazocin-2,6-diones could be synthesized through palladium-catalyzed carbonylation of 2-iodoanilines [22], reductive-cyclization of benzoyl azides [23], a base-promoted dimerization of anthranilic acid derivatives [24–27], and MsCl-mediated dimerization of anthranilic acid [28]. Moreover, there have been many synthetic routes to dibenzodiazocine derivatives developed. The Tang and Li group developed the base-promoted protocol for the construction of an eight-membered ring using o-aminobenzonitrile or o-phenylenediamine/phthalonitrile derivatives [29]. Wan and co-workers reported an acid-medated dimerization of isocyanates intermediates generated from benzoyl azides [30]. Authors hypothesized that the mechanism involves intermolecular [2 + 2] cyclization between isocyanates and ketone moieties. Similar casade reactions involving unique mechanism using specific substrates or reagents have been reported. For instanse, Scandium Pentafluorobenzoate-catalyzed cascade reaction of o-aminobenzaldehydes with primary amines affords an aminal-type eight-membered ring [31]. Grignard reagents with o-aminobenzonitriles generates dianion intermediates, resulting rapid dimerization and production of an aminal-type eight-membered ring [32]. Combination use of gold catalyst [(JonPhosAuNCMe)SbF_6] and b-(2-aminophenyl)-a,b-ynones affords dibenzo [1,5]diazocines through selective *8-exo-dig* intramolecular hydroamination of alynes [33]. Although dimerization reaction of anthranilic acid derivatives forges an dibenzodiazocin-2,6-dione, application of the dimerization to total synthesis of pestasulfamides A (**1**) and B (**2**) has not yet been realized [34].

In our continuation of the impressive efforts to access heterocycles through aminative coupling reactions [35–37], we developed the one-pot synthesis of *trans*-chloroamidines through copper-catalyzed Ritter-type multicomponent reaction of unactivated alkenes with various nitriles using dichloramin-T as an electrophile [38]. As an extention of the Ritter-type reaction, we also developed Ritter-type reaction of anthranilic acids with various nitriles to afford quinazoline assisted by $POCl_3$

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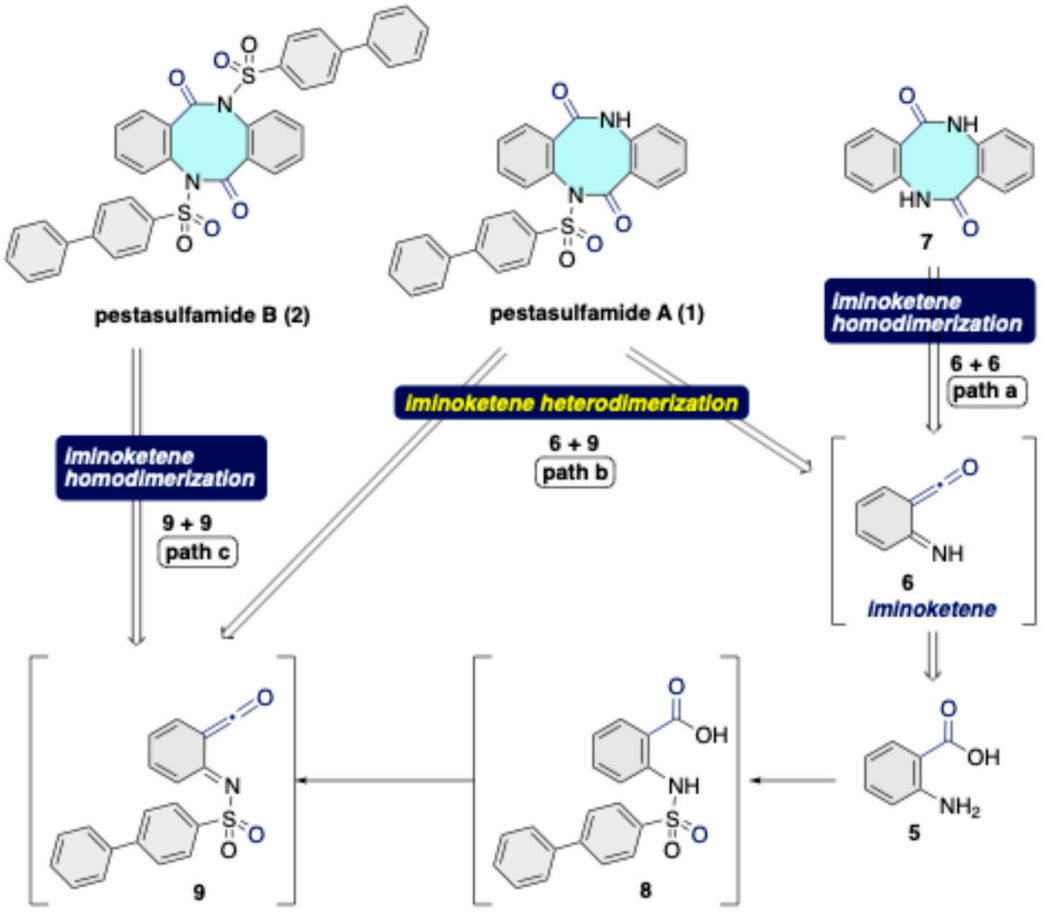
in the presence of copper-catalyst [39]. During this study, we encountered an unexpected dibenzodiazocin-2,6-dione, albeit low yield, through an iminoketen dimerization. Prompted by this unexpected observation, we envisioned that such an iminoketene dimerization strategy would be applicable to access pestasulfamides A (**1**) and B (**2**) if a suitable acid promotar is discovered. Herein, we report the first total synthesis of pestasulfamides A (**1**) and B (**2**) utilyzing the dimerization of anthranilic acid derivatives. Notably, this represents the first example of utilyzing iminoketen dimeriazation of anthranilic acids in natural product synthesis.

2. Results and Discussion

Building upon our previous observation in the Ritter-type reaction using anthranilic acid (**5**) with $POCl_3$, we envisioned the production of *N,N'*-unsubstituted benzodiazocine **7,** and pestasulfamides A (**1**) and B (**2**) by acid-promoted divergent iminokete dimerizations through *path a* (NH-iminoketene **6**), *path b* (iminoketenes **6** and **9**), and *path c* (N-substituted iminokete **9**), respectively (Scheme 1). The assembly of anthranilic acid (**5**) and 4-phenylbenzenesulfonyl chloride would lead to N-substituted iminokete **9** through sulfonamide **8**, simultaneously. Then, dimerization of N-substituted iminokete **9** occurs to produce pestasulfamides B (**2**) (path c). The timing of in-situ sulfonylation of amine moieties play an important role in our envisioned transformations.



Scheme 1. Retrosynthetic analysis of synthesis of pestasulfamides A (**1**) and B (**2**).

To assess the feasibility of this synthetic blueprint, we tested our synthetic blueprint with anthranilic acid (**5**) and 4-phenylbenzenesulfonyl chloride as a promoter for generation of iminoketene intermediate in pyridine at room temperature (Table 1). An equimolar amount of 4-phenylbenzenesulfonic chloride relative to anthranilic acid led to low conversion, affording products **1** and **2** in 21% and 8% (dimer yields), respectively (run 1). Contrary to expectations, benzodiazocine **7** was not detected from the reaction mixture, presumably due to less efficient dimerization of

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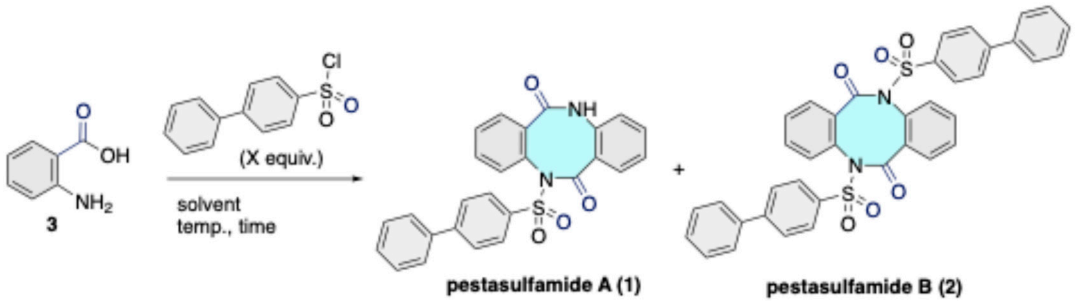
unsubstituted iminoketene **6**. This observation suggests that N-sulfonylation of anthranilic acid play an important role to promote the expected dimerization. Thus, we next investigated 4-phenylbenzenesulfonic chloride-to-substrate **5** ratio. Further investigations revealed that the amount of sulfonyl chloride played an important role in operating our transformation. The use of 1.5 equiv of 4-phenylbenzenesulfonic chloride afforded products **1** and **2** in 33% and 16%, respectively (run 2). The use of 2. equiv of 4-phenylbenzenesulfonic chloride was most effective, resulting in isolation of products **1** and **2** in 47% and 37%, respectively (run 3). Neither increasing 4-phenylbenzenesulfonic chloride to 2.5 equiv nor increasing it to 3.0 equiv slightly diminished the product yield, presumably due to the solubility issue (runs 4 and 5). Next, we investigated the impact on temperature on the reaction outcome (runs 6–8). The drop of temperature (0 °C) led to reduced yields (run 6). Whereas, increasing temperature has no discernible impact on the product yields (runs 7 and 8). Notably, the reaction rate did not be affected by reaction temperature. Solvents have a great impact on the reaction outcome. No products **1** and **2** were afforded by using other solvents such as Et_3N, AcOEt, THF, and DMSO (runs 9–12). These results revealed that pyridine is required to operate our transformation. Of the co-solvents screened (runs 13–15), pyridine/THF system (1/1, v/v) proved slight improved yields (run 13).

Table 1. One-pot cascade reaction of anthranilic acid (**3**) towards pestasulfamides A (**1**) and B (**2**).



Run[a]	PhBsCl (X equiv.)	Solvent (0.2 M)	Temp. (°C)	Time (h)	Yield (%) of **1**[b]	Yield (%) of **2**[b]
1	1.0	pyridine	rt	0.1	21	8
2	1.5	pyridine	rt	0.1	33	16
3	**2.0**	**pyridine**	**rt**	**0.1**	**47**	**37**
4	2.5	pyridine	rt	0.1	40	39
5	3.0	pyridine	rt	0.1	35	20
6	2.0	pyridine	0	0.1	34	41
7	2.0	pyridine	60	0.1	46	45
8	2.0	pyridine	reflux	0.1	50	40
9	**2.0**	Et_3N	rt	24	0	0
10	2.0	AcOEt	rt	24	0	0
11	2.0	THF	rt	24	0	0
12	2.0	DMSO	rt	24	0	0
13	2.0	**pyridine/THF (1/1, v/v)**	**rt**	**0.1**	**50**	**41**
14	2.0	pyridine/DMSO (1/1, v/v)	rt	0.1	23	16
15	2.0	pyridine/DMF (1/1, v/v)	rt	0.1	0	15

[a] Reaction conditions: Anthranilic acid (**3**) (1.0 mmol) and PhBsCl (X mmol, X equiv.) in solvent (5.0 mL, 0.2 M) under Ar. [b] Isolated yields.

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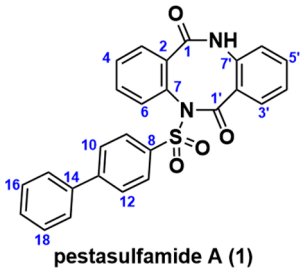
In isolation paper by Sun and She group, 2D NMR experiments of pestasulfamides A (**1**) and B (**2**) were insufficient due to the limit quantity of pestasulfamides A (**1**) and B (**2**) (A: 1.9 mg, B: 2.4 mg), while the structure of pestasulfamide B (**2**) was confirmed by X-ray analysis. With a sufficient amount of products with the purity acceptable for the NMR studies in hand, we conducted 2D NMR experiments. The spectroscopic data obtained for the synthetic sample of products **1** and **2** were identical to those reported for isolated pestasulfamides A (**1**) and B (**2**) (Tables 2 and 3). By the 2D NMR studies, full NMR assignment of pestasulfamides A (**1**) and B (**2**) could be presented (Supplementary Materials).

Table 2. Comparison of ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) data in $CDCl_3$ for synthetic sample **1** and ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data for natural pestasulfamide A.



pestasulfamide A (1)

position	synthetic **1** δ_H mult (*J* in Hz) 600 MHz, $CDCl_3$	natural **1** δ_H mult (*J* in Hz) 600 MHz, $CDCl_3$	synthetic **1** δ_C 151 MHz, $CDCl_3$	natural **1** δ_C 150 MHz, $CDCl_3$
1			158.1	165.6
2			116.7	119.6
3	8.24, dd (1.2, 7.8)	7.93, dd (1.5, 8.1)	129.0	126.8
4	7.60, td (1.2, 8.4)	7.48, overlap	129.3	129.2
5	7.91, m	7.50, overlap	137.3	137.3
6	7.78, t (9.0)	7.62, m	126.8	116.8
7			145.0	139.9
8			138.1	143.7
9	7.91, m	7.71, overlap	127.8	128.7
10	7.57, d (8.7)	7.90, overlap	127.8	127.8
11			146.1	145.1
12	7.57, d (8.7)	7.90, overlap	127.8	127.8
13	7.91, m	7.71, overlap	127.8	128.7
14			139.1	146.2
15	7.50, m	7.57, overlap	127.3	128.7
16	7.42, t (7.8)	7.44, overlap	129.1	129.3
17	7.38, tt (1.1, 9.9)	7.38, overlap	128.7	127.4
18	7.42, t (7.8)	7.44, overlap	129.1	129.3
19	7.50, m	7.44, overlap	127.3	128.7
1′			157.2	163.4
2′			115.5	123.5
3′	8.19, dd (1.8, 7.8)	8.19, dd (1.5, 8.1)	129.9	129.9
4′	7.16, td (1.0, 8.7)	7.16, m	123.5	123.5

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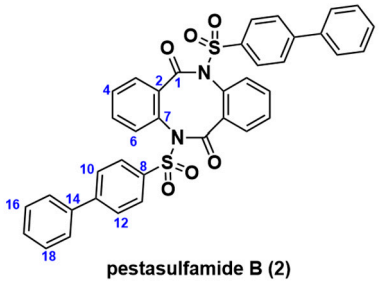
5′	7.50, m	7.52, overlap	134.3	134.3
6′	7.78, t (9.0)	8.25, dd (1.1, 7.9)	119.5	115.6
7′			139.8	138.2
1-NH	12.38, s	12.39, brs	---	---

Table 3. Comparison of ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) data in $CDCl_3$ for synthesis **2** and ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data for natural pestasulfamide B.



pestasulfamide B (2)

position	synthetic **2** δ_H mult (*J* in Hz) 600 MHz, $CDCl_3$	natural **2** δ_H mult (*J* in Hz) 500 MHz, $CDCl_3$	synthetic **2** δ_C 151 MHz, $CDCl_3$	natural **2** δ_C 125 MHz, $CDCl_3$
1			165.6	165.6
2			133.5	133.6
3	7.44, m	7.44, overlap	129.0	130.7
4	7.17, m	7.18, m	129.3	129.3
5	7.34, m	7.35, overlap	132.1	132.1
6	7.34, m	7.35, overlap	130.7	129.1
7			134.3	134.4
8			136.1	139.3
9	8.11, d (8.4)	7.77, d (7.9)	130.3	127.8
10	7.75, d (8.4)	8.13, d (7.9)	127.8	130.5
11			147.4	136.2
12	7.75, d (8.4)	8.13, d (7.9)	127.8	130.5
13	8.11, d (8.4)	7.77, d (7.9)	130.3	127.8
14			139.2	147.5
15	7.61, d (7.2)	7.62, d (7.2)	127.6	127.6
16	7.44, m	7.45, overlap	129.1	129.2
17	7.44, m	7.44, overlap	128.8	128.8
18	7.44, m	7.45, overlap	129.1	129.2
19	7.61, d (7.2)	7.62, d (7.2)	127.6	127.6

We then turned our attention to the timing of introduction of sulfonyl group. To gain further insight into the timing of the introduction of 4-phenylbenzenesulfonyl group on the dibenzodiazocine core, several additional experiments were conducted (Scheme 2). First, dibenzodiazocine 7 was subjected to the standard reaction conditions for 48 h, which resulted in no reaction (Scheme 2a). Furthermore, the reaction using possible intermediate **1** for pestasulfamide B (**2**) was conducted (Scheme 2b). To our surprise, no product was detected, thereby supporting the

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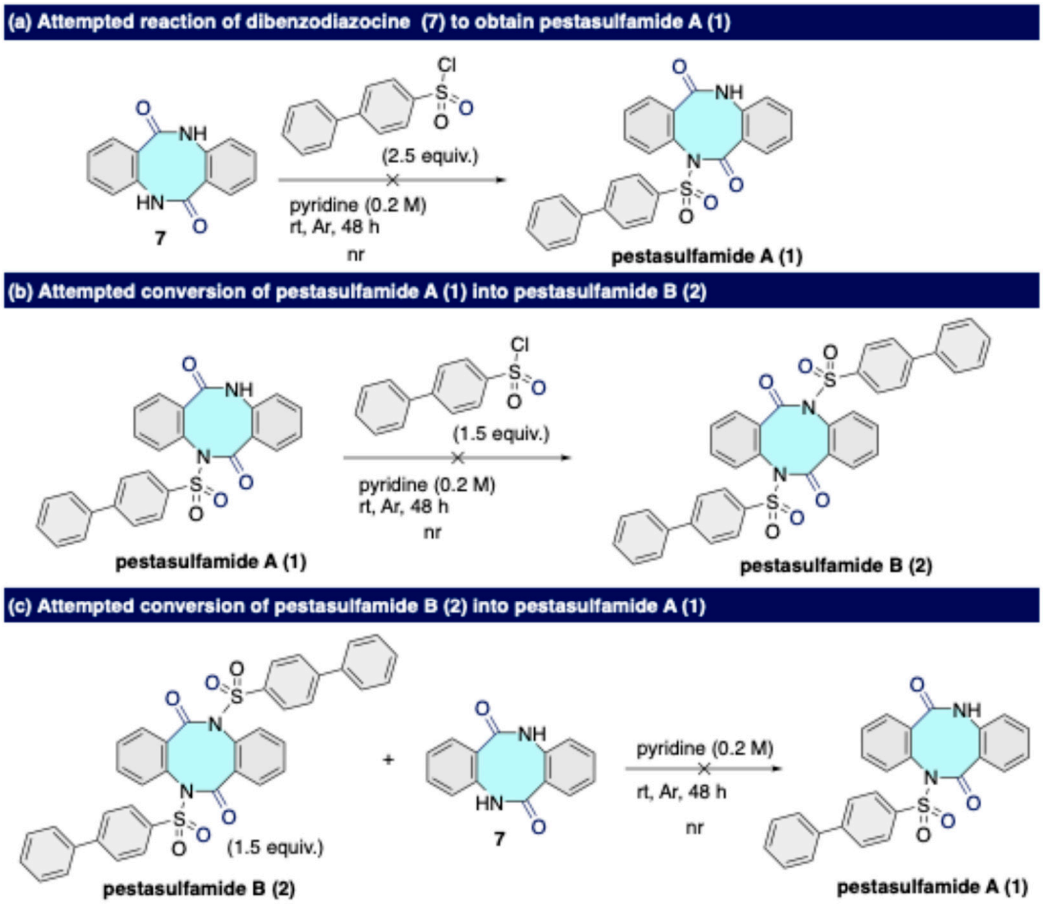
concerted dimerization mechanism. On these observations, late-stage transfer reaction of sulfonyl group using **2** and **7** was performed (Scheme 2c). In that case, we could not detect the desired product **1**, which would be produced by transfer of sulfonyl group from disulfonylated compound **2**. These results render the stepwise cyclization/gradual sulfonamidation pathway not feasible.



Scheme 2. Control experiments to elucidate the reaction mechanism.

3. Materials and Methods

3.1. General Information

Column chromatography was carried out using silica gel (WAKO Gel 75–150 mesh, WAKO Co., Ltd.). Preparative tin-layer chromatography was performed with silica gel plates (60F-254). Melting points (mp) were recorded with a Yamato melting point apparatus model MP-21 and are uncorrected. IR spectra were measured with a HORIBA Fourier transform infrared spectrometer FT-720, and absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). NMR experiments were performed with JEOL JNM-ECZ600R (^1H NMR: 600 MHz, ^{13}C NMR: 151 MHz) spectrometer and Varian NMR system 600 (^1H NMR:600 MHz, ^{13}C NMR: 151 MHz) spectrometer. Chemical shifts are expressed in δ [parts per million (ppm)] values, and coupling constants are expressed in hertz (Hz). ^1H NMR spectra were referenced to a solvent signal ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm). ^{13}C NMR spectra were referenced to a solvent signal ($CDCl_3$: 77.1 ppm, DMSO-d_6: 39.5). Signal multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublets (dd), triplet of doublets (td), and triplet of triplets (tt). High-resolution MS spectra were recorded with a Brucker microTOF mass spectrometer (ESI-TOF-MS). Reactions were monitored by thin layer chromatography (TLC) carried out on a silica gel plate (60F-254) and visualized under UV illumination at 254 or 365 nm, depending on the compounds. All substrates were used as received

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from commercial suppliers (Sigma-Aldrich, Kanto Chemical, TCI, Wako, and Nacalai Tesque), and all reagents were weighed and handled in air at room temperature.

3.2. Experimental Procedures and Characterization Data for the Synthetic Products

3.2.1. Synthesis of Pestasulfamide A (1) and Pestasulfamide B (2).

To a solution of **5** (137 mg, 1.0 mmol) in pyridine (5.0 mL, 0.2 M) was added 4-biphenylsulfonyl chloride (505 mg, 2.0 equiv., 2.0 mmol) under Ar atmosphere. The mixture was stirred at room temperature for 0.1 h. After the addition of 0.1 M HCl (20 mL), the whole was extracted with AcOEt (3 x 20 mL). The combined organic layer was extracted with sat. $NaHCO_3$ (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using hexane / AcOEt [3/1 (v/v)] to give **1** (107 mg, 0.24 mmol, 47% yield) as a white solid and **2** (125 mg, 0.19 mmol, 37% yield) as a white solid.

5-([1,1'-Biphenyl]-4-ylsulfonyl)dibenzo[*b,f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (pestasulfamide A, **1**): Mp 273–275 °C dec.; IR (KBr) ν: 3539, 3093, 2979, 1711, 1653, 1564, 1498, 1282, 1093, 814 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 12.38 (s, 1H), 8.24 (dd, J = 7.8, 1.2 Hz, 1H), 8.19 (dd, J = 7.8, 1.8 Hz, 1H), 7.89–7.93 (m, 3H), 7.78 (t, J = 9.0 Hz, 2H), 7.60 (td, J = 8.4, 1.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.49–7.51 (m, 3H), 7.42 (t, J = 7.8 Hz, 2H), 7.38 (tt, J = 9.9, 1.1 Hz, 1H), 7.16 (td, J = 8.7, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 158.1, 157.2, 146.1, 145.0, 139.8, 139.1, 138.1, 137.3, 134.3, 129.9, 129.3, 129.1, 129.0, 128.7, 127.8, 127.3, 126.8, 123.5, 119.5, 116.7, 115.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{18}N_2O_4SNa$ 477.0880; found 477.0881.

5,11-Bis([1,1'-biphenyl]-4-ylsulfonyl)dibenzo[*b,f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (pestasulfamide B, **2**): Mp 214–216 °C, dec.; IR (KBr) *v*: 3032, 2970, 1732, 1564, 1481, 1450, 1367, 1244, 1173, 1080, 768 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.40–7.47 (m, 4H), 7.33–7.35 (m, 1H), 7.15–7.18 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 165.6, 147.4, 139.2, 136.1, 134.3, 133.5, 132.1, 130.7, 130.3, 129.3, 129.1, 129.0, 128.8, 127.8, 127.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{38}H_{26}N_2O_6S_2Na$ 693.1125; found 693.1129.

3.2.2. Preparation of Dibenzo[b,f][1,5]diazocine-6,12 (5H,11H)-dione (7).

To the suspension NaH (1.6 g, 2.0 equiv., 40 mmol) in anhydrous THF (80 mL, 0.25 M) was added dropwise methyl 2-aminobenzoate (2.562 mL, 20 mmol) under Ar atmosphere. The mixture was stirred and heated to reflux for 3 days. The whole mixture was cooled to room temperature and then poured slowly into 0.1 M HCl with ice. After the ice melted, the precipitated product was collected by filtration, washed several times with H_2O and AcOEt to yield **7** as a white solid (1.55 g, 6.5 mmol, 65% yield). Mp 327–329 °C, dec.; IR (KBr) *v*: 3244, 3167, 1678, 1633, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.21 (s, 2H), 7.34 (td, J = 9.0, 1.4 Hz, 2H), 7.31 (dd, J = 7.5, 1.5 Hz, 2H), 7.23 (dt, J = 7.8, 0.6 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 169.3, 134.8, 133.6, 130.6, 128.2, 127.3, 125.8; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{10}N_2O_2Na$ 261.0635; found 261.0639.

4. Conclusions

In summary, we have successfully achieved the first total synthesis of pestasulfamides A (**1**) and B (**2**) in one-pot protocol. A proof-of-concept for divergent synthesis of substituted dibenzodiazocines utilizing iminoketene dimerization has been demonstrated. The key transformation features an iminoketene dimeriazation of anthranilic acid triggered by a sulfonylation in a pyridine/THF system. These findings highlight the powerfulness of sulfonylation driven iminoketene dimerization in accessing complex dibenzodiazocines.

Supplementary Materials: The following are available online; ^1H- and ^{13}C-NMR charts of all the compounds, and 2D-NMR charts of **1** and **2**.

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