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Development of an Efficient Synthetic Process for Broflanilide

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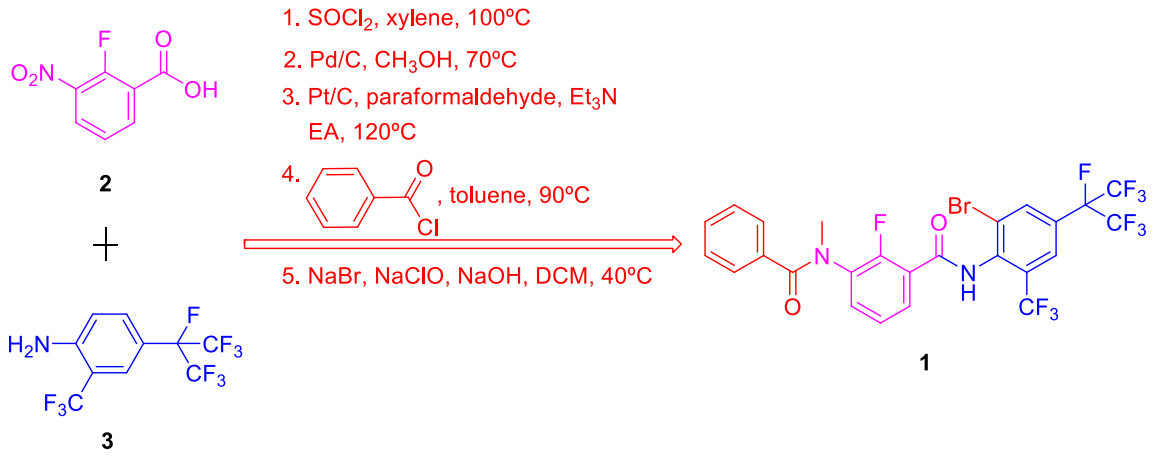
TOC graphic:

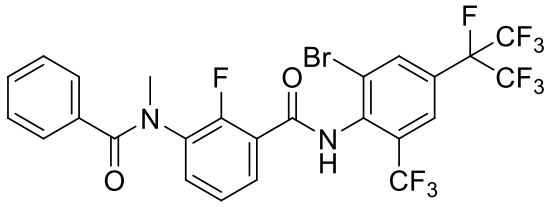

1. SOCl2, xylene, 100°C
2. Pd/C, CH3OH, 70°C
3. Pt/C, paraformaldehyde, Et3N
EA, 120°C
4. , toluene, 90°C
5. NaBr, NaClO, NaOH, DCM, 40°C
2
3
1

ABSTRACT: This article describes the development of an efficient and scalable synthetic route to the novel insecticide broflanilide (**1**). This redesigned synthetic sequence starts from 2-fluoro-3-nitrobenzoic acid and 4-(perfluoropropan-2-yl)-2-(trifluoromethyl) aniline and provides the target product in a high overall yield through condensation, nitro group reduction, *N*-methylation, amidation and subsequent bromination steps. The desired amide moiety is established under mild conditions, and imide generation is avoided. Using paraformaldehyde and Pt/C for *N*-methylation and NaBr-NaClO for bromination increased the industrial suitability of this route. Unlike existing routes, this new route requires isolation at only six steps (including the heptafluorination), and the overall yield was 60.3%, representing a significant improvement. Broflanilide (**1**) crystals were obtained from recrystallization in 98% aqueous CH_3OH, and the structure was confirmed by X-ray analysis. This work provides a reliable strategy for the large-scale manufacturing of broflanilide (**1**).

KEYWORDS: broflanilide, insecticides, synthesis, crystal structure

INTRODUCTION

Insects are one of the most important causes of crop yield reduction in recent decades, and the annual economic loss caused by arthropod pests alone exceeds 400 billion USD.[1] With the development of insecticide resistance, this situation will worsen.[2] Thus, to facilitate insecticide resistance management in agriculture and meet the food demands of the rapidly growing population (expected to reach 9 billion by 2050), new insecticides with unique modes of action are essential.[3] Broflanilide (**1**; Fig. 1), discovered by Mitsui Chemicals, is an efficient broad-spectrum meta-diamide insecticide.[4] Its active metabolite, desmethyl-broflanilide, acts on or close to G336, a novel site in the M3 region of drosophila resistant-to-dieldrin (RDL) γ-aminobutyric acid (GABA) receptor, inhibiting the permeation of chloride ions and GABA-induced neuroactivity and thus resulting in hyperexcitation and death. The binding site is different from that of conventional noncompetitive antagonists (NCAs), making **1** active against cyclodiene-resistant and fipronil-resistant pests. In addition, the selectivity of desmethyl-broflanilide for pests over mammals makes it safer.[5] Accordingly, **1** is one of most promising insecticides in recent decade, and it is sure to be a powerful pest control agent after its commercialization in 2020. To accelerate its practical application in agriculture, an economical, efficient and scalable synthetic process is required. Herein, a new synthetic route to **1** was designed and optimized, including the synthesis of intermediates as well as the drug substance.



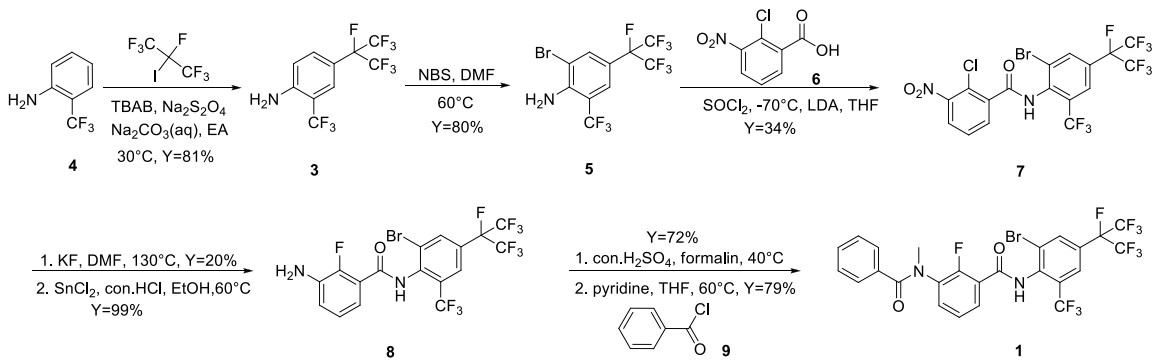
1

Figure 1. Broflanilide (**1**)

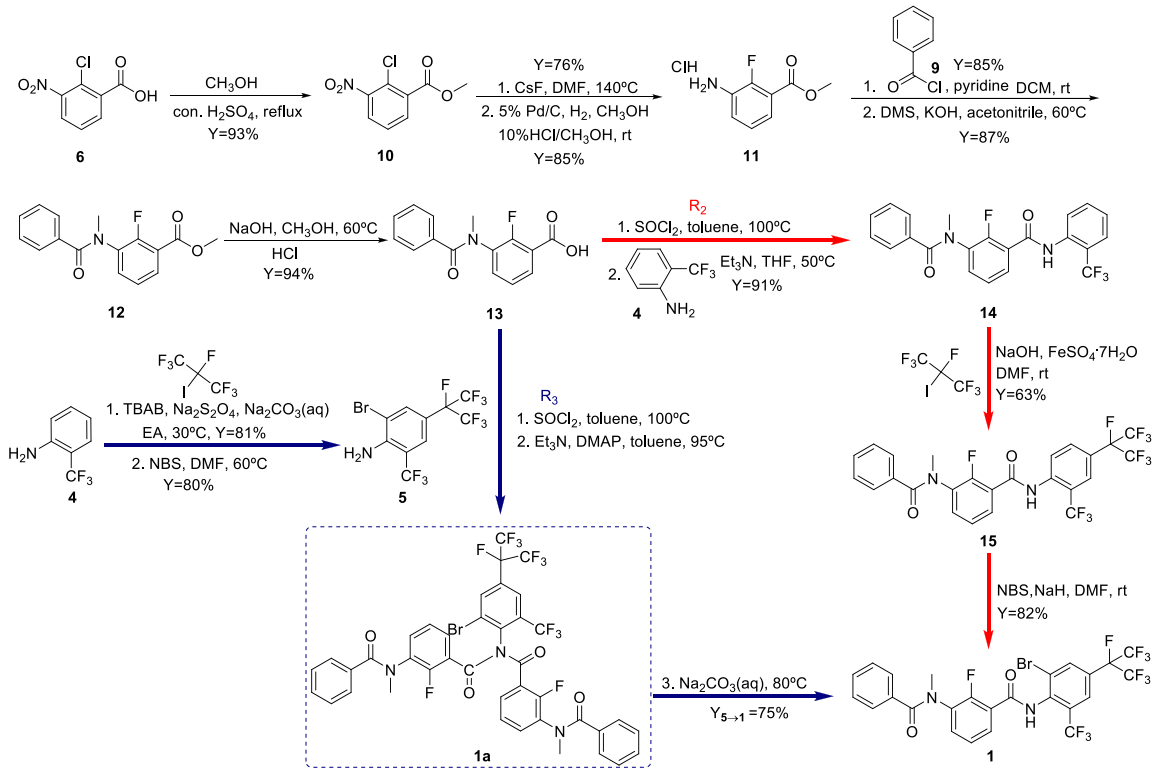
RESULTS AND DISCUSSION

Existing routes. In recent years, several methods for the synthesis of broflanilide (**1**) have been reported (as shown in Scheme 1 and Scheme 2).[6,7] Scheme 1 (route R1) successfully provided **1** in a 2.5% overall yield to support early research. However, key intermediate **7** needed to be prepared in the presence of lithium diisopropylamide (LDA) at a low temperature (-70℃), and this synthesis required purifications with silica gel chromatography. In Scheme 2, route R2 and route R3 afforded high quality **1** through relatively mild reaction conditions, with overall yields of 19.6% and 20.3%, respectively. However, there were several opportunities to improve these two processes. In route R2, the bromination to convert intermediate **15** to **1** required the hazardous reagent sodium hydride, which is not always easy to handle on a large scale.[8] In route R3, imide **1a** was the main product of the condensation of benzoic acid **13** and bromoaniline **5**, which necessitated cumbersome operations including multiple cycles of alkali decomposition to obtain **1** and the recovery of benzoic acid **13**.[9] In addition, during the synthesis of the common intermediate benzoic acid **13** in both route R2 and route R3, highly toxic dimethyl sulfate (DMS)[10] was employed in the *N*-methylation reaction, and some benzoic acid **13** was decomposed during the synthesis of the acid chloride, thus resulting in impurities.

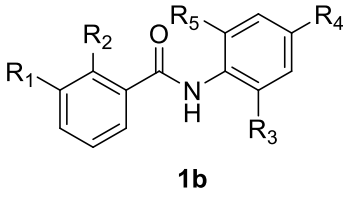
Scheme 1. Initial synthetic route R1 to **1**.



Scheme 2. Synthesis of **1** via route R2 and route R3**.**



Alternative Route. After meticulous evaluation of the existing routes, we determined that an alternative route was necessary to manufacture **1**. The keys to this route were (a) development of a method for building the core structure **1b** (Fig. 2) that avoided imide generation and harsh reaction conditions and (b) development of appropriate *N*-methylation and bromination methods that avoided the use of hazardous reagents. Moreover, an adjustment of the reaction sequence was necessary due to the tedious and relatively low yields of the existing routes.



1b

R_1 = NO_2, $N(CH_3)COPh$ R_4 = $C(CF_3)_2F$, H

R_2 = Cl, F R_5 = Br, H

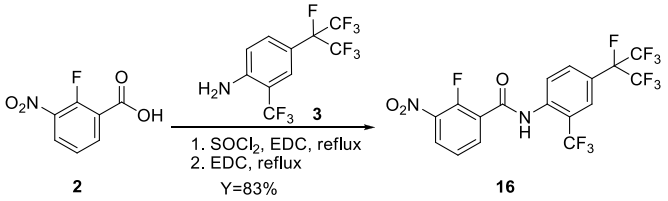
R_3 = CF_3, H

Figure 2. The core structure of broflanilide (**1**).

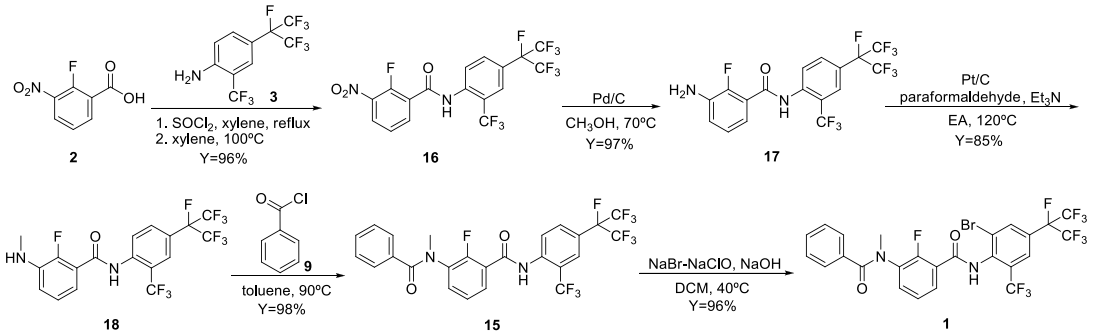
At the beginning of our exploration of alternative routes, we focused on the synthesis of core structure **1b** and made many attempts toward its production. Among these attempts, the one based on the relatively short route (R1) provided encouraging results—namely, the condensation of 2-fluoro-3-nitrobenzoic acid (**2**) and unbrominated aniline **3**[11] in

dichloroethane (EDC) smoothly formed nitroamide **16** (83% yield) (Scheme 3). This method avoided the harsh reaction conditions required for the condensation in route R1 and showed no imide generation, providing an ideal path for the development of an alternative route. For the subsequent reaction steps, the feasibility of the bromination step in route R2 provided a reliable reference and prompted us to design and optimize an alternative route based on the following reaction sequence: condensation, nitro group reduction, *N*-methylation, benzamide and bromination (Scheme 4).

Scheme 3. Condensation reaction of 2-fluoro-3-nitrobenzoic acid with aniline **3**.



Scheme 4. The alternative route for the synthesis of **1**.



Synthetic Process. Although nitroamide **16** was successfully obtained as previously described, the reaction was not complete after 24 h under these conditions, and thus, this step required further optimization.

The reaction was carried out in a range of conventional solvents, and the results were screened. Toluene and xylene were found to perform better than EDC, and 93-95% yields could be obtained at reflux (Table 1, entries 1-3). In addition, the yield achieved with xylene was inferior to that achieved with toluene due to the increase of impurity (Table 1, entries 2 and 3). These results indicated that the temperature was the key factor in this condensation reaction. Therefore, we adjusted the temperature of the reaction with xylene to the reflux temperature of toluene (110°C) and obtained a reaction result similar to that obtained with toluene (Table 1, entries 2 and 4). Considering its relatively low toxicity, xylene was selected as the optimal solvent.[12] When the reaction temperature was reduced to 100°C, the best yield (96%) was obtained, and at lower reaction temperatures, such as 90°C, the reaction was not complete after 10 h (Table 1, entries 5 and 6). Therefore, 100°C was selected as the optimal reaction temperature. Under the optimal conditions, the reaction was completed after 5 h. After increasing the amount of xylene, the reaction solution was washed with sodium carbonate (5 wt% aq) to remove the excess acid. Then,

the organic layer was separated and cooled to 5°C, and intermediate **16** was precipitated and collected by filtration in a 96% yield with 99% purity. Thus, a method to directly construct the desired amide structure **1b** using mild reaction conditions and simple operations has been achieved.

Table 1. Optimization of the reaction conditions for **2** and **3**.[a]

Entry	Solvent	Temp (°C)	Time (h)	HPLC area (%)		Yield[c] of **16** (%)
				16	Impurity[b]	
1	EDC	Reflux (83)	24	86.00	ND[d]	83
2	Toluene	Reflux (110)	5	97.70	0.89	95
3	Xylene	Reflux (140)	5	95.63	2.93	93
4	Xylene	110	5	97.90	0.85	95
5	Xylene	100	5	98.50	0.21	96
6	Xylene	90	10	93.15	ND[d]	91

[a]All reactions were carried out with 0.05 mol of **3** and 0.053 mol of **2** in 19 mL of solvent. [b]Preliminary LC/MS analysis showed that the impurity contained the same molecular weight as nitroamide **16**. [c]Isolated yield. [d]Not detected.

With nitroamide **16** in hand, the synthesis of aminoamide **17** was attempted using a classic nitro reduction approach catalyzed by Pd/C under 2.0 MPa hydrogen pressure.[13] Upon reaction completion, the reaction solution was cooled to room temperature and filtered, and the filtrate was concentrated to afford aminoamide **17**. Screening revealed that the reaction could be carried out in a variety of solvents, including toluene, xylene, CH_3OH and ethyl acetate (Table 2). The highest yield 97% was provided when CH_3OH was used as a solvent.

Table 2. Comparison of the nitro reducing solvents for nitroamide **16**.[a]

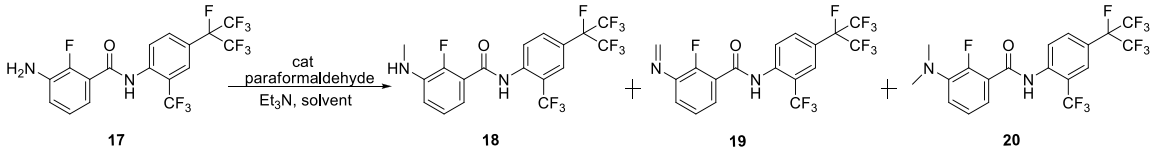
Entry	Solvent	Yield[b] (%)
1	Toluene	56
2	Xylene	74
3	CH_3OH	97
4	Ethyl acetate	93

[a]All reactions were carried out with 0.05 mol of nitroamide **16**, 5 wt‰ of Pd/C relative to **16**, and 2.0 MPa hydrogen pressure at 70°C for 9 h. [b]Isolated yield.

With conditions to arrive at amino amide **17** in hand, we turned our attention to the *N*-methylation reaction. To avoid the use of highly toxic reagents, we tried to use paraformaldehyde as the methylation reagent, as it is inexpensive and less toxic.[14] The N-methylation results using different catalysts in ethyl acetate as the solvent under a 2.5

MPa hydrogen pressure are listed in Table 3. Intermediate **18** was not obtained when aluminum powder was used as the catalyst (Table 3, entry 2). When Raney nickel was used, only a small amount of **18** was generated; 12% (HPLC area) of defluorinated **17** as well as 6% (HPLC area) of defluorinated **18** were observed (Table 3, entry 3). The Pd/C catalytic system could provide intermediate **18** with low selectivity (Table 3, entry 1). The best result (90% by HPLC analysis) was obtained under Pt/C catalysis (Table 3, entry 4). As expected, no product was obtained in the absence of catalyst (Table 3, entry 9). In addition, a solvent screening indicated that isopropanol, toluene and CH_3OH-ethyl acetate cannot promote the transformation (Table 3, entries 5-7). CH_3OH seemed to be useful for the formation of Schiff base **19** (Table 3, entry 8). Therefore, Pt/C and ethyl acetate were selected as the optimal conditions. The reaction was carried out under optimal conditions, and after completion, the solution was filtered.[15] The filtrate was concentrated and *N*-methylamide **18** (85% yield, 98% purity) was separated from the concentrated residue by recrystallization in xylene solvent.

Table 3. Screening of *N*-methylation reaction conditions.[a]



17 18 19 20

Entry	Catalyst	Solvent	HPLC area %		
			18	**19**	**20**
1	Pd/C	Ethyl acetate	25	40	30
2	Aluminum powder	Ethyl acetate	--[b]	--[b]	--[b]
3	Raney Nickel	Ethyl acetate	30	2	2
4	Pt/C	Ethyl acetate	90	3	2
5	Pt/C	Isopropanol	50	2	3
6	Pt/C	Toluene	55	3	3
7	Pt/C	CH_3OH - Ethyl acetate	45	2	9
8	Pt/C	CH_3OH	11	70	7
9	/	Ethyl acetate	--[b]	--[b]	--[b]

[a]All reactions were performed using aminoamide **17** (0.05 mol), Et_3N (0.12 g), 15 mL of solvent, 2 wt‰ catalyst relative to **17**, maintaining a hydrogen pressure of 2.5 MPa and reacting at 120°C for 9 h. [b]Not detected.

Meta-diamide **15** was prepared by the acyl halide method, which involved the condensation of *N*-methylamide **18** with benzoyl chloride (**9**) at 90°C, and the reaction was efficient and operationally simple. Upon completion of the reaction, sodium carbonate (5 wt% aq) was slowly added to the solution to remove excess benzoyl chloride

(**9**), and then the organic layer was separated. After the organic layer was concentrated under reduced pressure, the residue containing **15** was diluted with dichloromethane and used directly in the bromination step. The equivalents of benzoyl chloride (**9**) were screened, and the results indicated that decreasing the number of equivalents would decrease the yield of meta-diamide **15** (Table 4, entry 1). It is likely that some of the benzoyl chloride (**9**) was hydrolyzed during the reaction, and thus, it had to be used in excess relative to *N*-methylamide **18** for the reaction to go to completion. The best yield (98%) was obtained by using 1.05 equiv. of **9** relative to **18** (Table 4, entry 2).

Table 4. Comparison of the amount of benzoyl chloride **9** used to form meta-diamide **15**.[a]

Entry	Equiv of **9**	Yield[b] (%)
1	1.00	94
2	1.05	98
3	1.10	98

[a]All reactions were carried out with 0.05 mol of *N*-methylamide **18** at 90°C for 3 h. [b]Isolated yield.

Referring to route R2, the bromination step was designed as the last step of the alternative route. Here, we attempted to employ a bromination process that was economical and operationally simple. As HBr-H_2O_2 and NaBr-NaClO are generally considered to be relatively economical bromination reagents[16], they were tried in the bromination reaction first with dichloromethane (DCM) as the solvent. The reaction results indicated that HBr-H_2O_2 did not provide any products (Table 5, entry 1), while NaBr-NaClO gave a satisfactory result, providing **1** in a 96% yield (Table 5, entry 2). We found that when toluene was used as the solvent, the yield of the product slightly decreased (Table 5, entry 3). This may be because small amounts of new impurities were formed in the toluene. In addition, due to the low solubility of **1** in toluene, the amount of solvent had to be increased during reaction work-up to prevent **1** from precipitating. As shown in Table 5, reducing the reaction temperature slowed the reaction and increased the required reaction time. For example, 7 h was needed to complete the reaction when the reaction temperature was decreased to 20°C (Table 5, entry 5). Therefore, NaBr-NaClO was selected as the optimal bromination reagent, and the optimal temperature was 40°C (reflux), while the optimal solvent was DCM. Upon reaction completion, the organic layer was separated when it was hot, and sodium sulfate (5 wt% aq) was added. The resulting solution was acidified with concentrated hydrochloric acid. The newly formed layers were separated, and the resulting organic layer was concentrated to obtain crude **1**.

Table 5. Screening the bromination reaction conditions for meta-diamide **15**.[a]

Entry	Bromine source	Solvent	Temp (°C)	Time (h)	Yield[b] (%)

1	HBr-H_2O_2[c]	DCM	Reflux (40)	6.0	NA[d]
2	NaBr-NaClO	DCM	Reflux (40)	1.0	96
3	NaBr-NaClO	Toluene	40	1.0	94
4	NaBr-NaClO	DCM	30	4.5	92
5	NaBr-NaClO	DCM	20	7.0	91

[a]The amount of meta-diamide **15** was 0.05 mol, and 60 g of solvent was used in all reactions. [b]Isolated yield. [c]2,2'-Azobis(2-methylpropionitrile) as an initiator. [d]Not available.

Recrystallization of broflanilide (1). Considering the importance of recrystallization in the development and application of drugs[17] and to validate the structure of our product, we tried to obtain **1** in a crystalline form. The best solvent for recrystallization was defined by screening the solubility of **1** in a range of solvents, including DMF, DCM, diethyl ether, methanol, ethyl alcohol, acetone, isopropanol and the mixed solvents of ethanol-water, methanol-water and isopropanol-water. The results indicated that 98% aqueous CH_3OH was the best solvent for the recrystallization of **1**. These optimal conditions provided **1** in a high purity (99.2%) via this alternative route. The molecular structure of **1** was confirmed by X-ray analysis of the crystal.

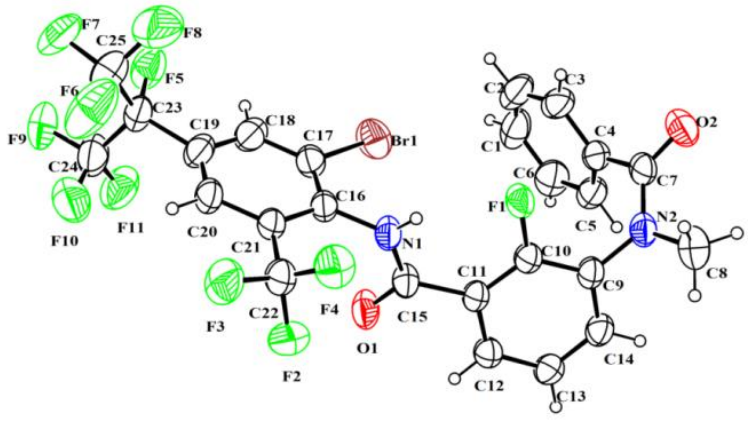


Figure 3. Molecular structure of broflanilide (**1**) obtained from X-ray analysis.

CONCLUSION

The development of an efficient synthetic route to the meta-diamide insecticide broflanilide (**1**) has been successfully achieved. In the new route, 2-fluoro-3-nitrobenzoic acid (**2**) and 4-(perfluoropropan-2-yl)-2-(trifluoromethyl)aniline (**3**) were the starting materials, and the key amide frame was successfully established under mild reaction conditions. The use of paraformaldehyde and Pt/C avoided highly toxic reagents, and the use of NaBr-NaClO as the brominating reagent increased the industrial feasibility of this route. Additionally, the synthetic sequence was redesigned to afford broflanilide (**1**) in six steps (including the heptafluorination step), and the overall yield was 60.3%, representing a significant improvement. Intermediates **16**, **17**, and **18** were synthesized as new chemical compounds, and the molecular structure of broflanilide (**1**) was confirmed by X-ray crystallography.

EXPERIMENTAL SECTION

General. All reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer. J values are given in Hertz. Mass spectra were recorded on a Q-ExactiveTM spectrometer. HPLC separations were performed on a Shim-pack GIST C_{18} column, and the specific analysis methods are as follows.

*HPLC Method for Intermediate **16**.* Shim-pack GIST C_{18}, 150×4.6 mm, 5 μm, isocratic elution with 70:30 CH_3OH/0.1% H_3PO_4 in H_2O over 20 min, 1.5 mL/min flow at 40°C with detection at 240 nm. HPLC retention time: **16** = 11.80 min.

*HPLC Method for Intermediate **17**.* Shim-pack GIST C_{18}, 150×4.6 mm, 5 μm, isocratic elution with 70:30 CH_3OH/0.1% H_3PO_4 in H_2O over 20 min, 1.5 mL/min flow at 40°C with detection at 240 nm. HPLC retention time: **17** = 10.80 min.

*HPLC Method for Intermediate **18**.* Shim-pack GIST C_{18}, 150×4.6 mm, 5 μm, isocratic elution with 75:25 CH_3OH/0.1% H_3PO_4 in H_2O over 20 min, 1.5 mL/min flow at 40°C with detection at 240 nm. HPLC retention time: **18** = 10.38 min.

*HPLC Method for Intermediate **15*** Shim-pack GIST C_{18}, 150×4.6 mm, 5 μm, isocratic elution with 75:25 CH_3OH/0.1% H_3PO_4 in H_2O over 25 min, 1.5 mL/min flow at 40°C with detection at 240 nm. HPLC retention time: **15** = 11.61 min.

*HPLC Method for Product **1**.* Shim-pack GIST C_{18}, 150×4.6 mm, 5 μm, isocratic elution with 75:25 CH_3OH/0.1% H_3PO_4 in H_2O over 15 min, 1.5 mL/min flow at 40°C with detection at 240 nm. HPLC retention time: **1** = 7.54 min.

2-Fluoro-3-nitro-N-(4-(perfluoropropan-2-yl)-2-(trifluoromethyl)phenyl)benzamide (16). To a stirring solution of **2** (400 g, 2.1 mol) in xylene (0.9 L) at 25°C, $SOCl_2$ (378 g, 3.15 mol) and DMF (2 mL) were added. The solution was stirred at reflux for 2 h. After concentration, **3** (686 g, 2 mol) and xylene (0.8 L) were added, and the solution was stirred for 5 h at 100°C. Upon reaction completion, xylene (2.4 L) and 5 wt% aqueous sodium carbonate (800 g) were slowly added, and the resulting solution was agitated for

30 min at 80°C. The organic layer was separated while hot and cooled to 5°C. The solid was collected by filtration and dried at 50°C to afford **16** as a white solid (959.94 g, 99% purity, 96%, yield from **3**). MS $[M - H]^-$ m/z calcd 495.0203, found 495.0204. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.40 – 8.36 (m, 1H), 8.24 – 8.06 (m, 3H), 7.97 (d, J = 2.2 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.69, 152.49 (d, J = 263.7 Hz), 138.50, 137.99 (d, J = 8.3 Hz), 136.07 (d, J = 3.7 Hz), 131.72, 130.87 (d, J = 9.2 Hz), 128.82, 126.69 (d, J = 14.7 Hz), 126.44 (q, J = 31.0 Hz), 125.59 (d, J = 4.6 Hz), 124.37 (d, J = 20.9 Hz), 124.09 – 123.61 (m), 123.03 (q, J = 270.9 Hz), 118.99 (qd, J = 284.2, 27.4 Hz), 91.15 (dp, J = 201.0, 32.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.23 (d, J = 3.5 Hz), -75.32 (d, J = 7.6 Hz), -122.18 – -122.23 (m), -181.66 – -181.69 (m).

3-Amino-2-fluoro-N-(4-(perfluoropropan-2-yl)-2-(trifluoromethyl)phenyl)benzamide (17). Intermediate **16** obtained from the previous step, 5.0 wt% Pd/C (4.80 g, approximately 50% water) and CH_3OH (1.8 L) were combined in an autoclave. The atmosphere in the autoclave was displaced three times with nitrogen and then pressurized to 2 MPa with hydrogen. The reaction mixture was stirred at 70°C for 9 h while a hydrogen pressure of 2 MPa was maintained. After the reaction was complete, the reaction solution was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure to afford **17** (883.35 g, 98.2% purity, 97%, yield from **16**) as a white solid. MS $[M - H]^-$ m/z calcd 465.0461, found 465.0463. MS $[M + H]^+$ m/z calcd 467.0617, found 467.0617. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (d, J = 4.0 Hz, 1H), 8.09 (s, 2H), 7.92 (s, 1H), 7.10 – 6.94 (m, 2H), 6.90 - 6.86 (m, 1H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.46, 148.22 (d, J = 240.6 Hz) 139.28, 137.66 (d, J = 13.2 Hz), 131.11, 130.86 (d, J = 9.2 Hz), 125.70 (q, J = 30.1 Hz), 124.77 (d, J = 3.6 Hz), 123.98 – 123.62 (m), 123.21 (q, J = 270.9 Hz), 123.46 (d, J = 20.8 Hz), 123.12 (d, J = 11.2 Hz), 119.27 (d, J = 5.3 Hz), 120.44 (td, J = 284.2, 27.6 Hz), 116.30, 92.83 – 89.49 (m). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.18 (d, J = 3.4 Hz), -75.31 (d, J = 7.3 Hz), -136.86 – -136.92 (m), -181.67 – -181.69 (m).

2-Fluoro-3-(methylamino)-N-(4-(perfluoropropan-2-yl)-2-(trifluoromethyl)phenyl)benzamide (18). Intermediate **17** obtained from the previous step, paraformaldehyde (70.5 g, 2.23 mol), 5.0 wt% Pt/C (1.77 g, approximately 50% water), Et_3N (4.42 g) and ethyl acetate (0.49 L) were combined in an autoclave. The atmosphere in the autoclave was displaced three times with nitrogen and then pressurized to 2.5 MPa with hydrogen. The reaction solution was stirred at 120°C for 9 h while the hydrogen pressure was maintained. Upon reaction completion, the reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated, and the residue was recrystallized from xylene to afford **18** (774.82 g, 98% purity, 85%, yield from **17**) as a white solid. MS $[M - H]^-$ m/z calcd 479.0618, found 479.0616. MS $[M + H]^+$ m/z calcd 481.0774, found 481.0776. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (d, J = 3.7 Hz, 1H),

8.09 (s, 2H), 7.92 (s, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.98 – 6.77 (m, 2H), 5.99 – 5.80 (m, 1H), 2.78 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.04, 148.15 (d, J = 241.9 Hz), 138.85, 138.50 (d, J = 12.0 Hz), 130.72, 130.44 (d, J = 9.2 Hz), 125.30 (q, J = 30.4 Hz), 124.71 (d, J = 3.7 Hz), 123.71 – 123.17 (m), 123.08 (d, J = 20.9 Hz), 122.80 (q, J = 270.9 Hz), 121.99 (d, J = 10.9 Hz), 120.05 (qd, J = 284.1, 27.3 Hz), 114.87, 113.69 (d, J = 4.9 Hz), 93.27 – 88.70 (m), 29.60. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.35 (d, J = 3.5 Hz), -75.51 (d, J = 7.4 Hz), -136.98 (q, J = 3.7 Hz), -181.86 (dq, J = 14.8, 7.3 Hz).

2-Fluoro-3-(N-methylbenzamido)-N-(4-(perfluoropropan-2-yl)-2-(trifluoromethyl)phenyl)benzamide (15). Intermediate **18** obtained from the previous step and benzoyl chloride (**9**, 238 g, 1.66 mol) were added to toluene (1.8 L). The solution was stirred for 3 h at 90°C. After the reaction was complete, 5 wt% aqueous sodium carbonate (640 g) was slowly added to the reaction mixture. The resulting solution was stirred for 30 min at 80°C. The layers were separated while hot, and the organic layer was concentrated under reduced pressure. The residue, which contained **15** (927.13 g, 98%, yield from **18**), was diluted with dichloromethane (1.4 L) and used directly in the next step. A sample of purified **15** (white solid) was analyzed as follows. MS $[M - H]^-$ m/z calcd 583.0880, found 583.0878. MS $[M + H]^+$ m/z calcd 585.1036, found 585.1033. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.11 (dd, J = 8.7, 2.2 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 2.3 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.46 – 7.16 (m, 6H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.55, 163.30, 154.80 (d, J = 251.1 Hz), 138.87, 135.89, 133.40, 133.11 (d, J = 12.5 Hz), 131.80, 130.98 (d, J = 9.2 Hz), 130.35, 129.57 (d, J = 2.4 Hz), 123.88 (q, J = 5.7 Hz), 128.20 (d, J = 39.5 Hz), 126.42 (q, J = 30.5 Hz), 125.34 (d, J = 4.3 Hz), 124.40 (d, J = 13.3 Hz), 124.02 (d, J = 20.9 Hz), 123.08 (q, J = 271.2 Hz), 120.43 (qd, J = 284.1, 27.5 Hz), 98.25 – 84.31 (m), 37.72. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.19 (d, J = 4.4 Hz), -75.28 (d, J = 8.1 Hz), -123.34, -181.64 (dp, J = 17.5, 9.3, 8.6 Hz).

N-(2-Bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl)-2-fluoro-3-(N-methylbenzamido)benzamide (1). NaBr (241.4 g, 2.32 mol), NaOH (32.5 g, 0.78 mol) and water (400 g) were added to a solution of **15** (prepared in the previous step) in dichloromethane, and the resulting mixture was heated to 40°C (reflux). Then, 14 wt% aqueous sodium hypochlorite (1.24 kg, 2.33 mol) was added dropwise to the reaction solution. The resulting solution was stirred for 1 h at 40°C (reflux), and the layers were separated while hot. The organic layer was washed with 10 wt% aqueous sodium sulfite (480 g), and then, the pH of the aqueous layer was adjusted to approximately 4 with concentrated hydrochloric acid. The organic layer was separated and concentrated under reduced pressure to afford crude **1**. Crude **1** was recrystallized from 98% aqueous CH_3OH (870 g) and dried for 2 h at 90°C to give pure **1** (997.10 g, 99.2% purity, 96%, yield from **15**) as a white solid. MS $[M - H]^-$ m/z calcd 660.9985, found 660.9813. MS $[M + H]^+$ m/z calcd 663.0141, found 663.0149. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69

(s, 1H), 8.41 (s, 1H), 7.96 (s, 1H), 7.63 – 7.57 (m, 2H), 7.42 – 7.20 (m, 6H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.63, 163.10, 154.78 (d, J = 252.5 Hz), 139.24, 135.96, 134.47 (d, J = 10.7 Hz), 133.26, 133.17, 131.56 (q, J = 30.2 Hz), 130.29, 129.15 (d, J = 2.2 Hz), 128.16 (d, J = 39.1 Hz), 126.84 (d, J = 21.3 Hz), 125.28 (d, J = 4.4 Hz), 124.46 (d, J = 13.7 Hz), 123.09, 122.29 (q, J = 271.7 Hz), 120.24 (qd, J = 284.4, 27.3 Hz), 92.28 - 88.92 (m), 37.61. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.95, -74.89 (d, J = 8.5 Hz), -123.10, -180.86 – - 180.91 (m).

Preparation of 4-(perfluoropropan-2-yl)-2-(trifluoromethyl)aniline (3) according to the method mentioned in WO2019059412A1: To a mixture of O-trifluoromethylaniline (**4**, 488 g, 3 mol), tetrabutylammonium bromide (54 g, 0.16 mol), ethyl acetate (2.2 L), perfluoro-2-iodopropane (1.33 kg, 4.5 mol) and water (980 g), a solution of sodium dithionite (320 g, 1.65 mol) in 2.5 wt% aqueous sodium carbonate (1.25 kg, 0.3 mol) was added dropwise over 3 h at 30°C. During the addition of aqueous sodium dithionite, the pH of the aqueous layer was adjusted to approximately 4.4 with 18 wt% aqueous sodium carbonate. Then, the mixture was vigorously stirred for 3 h at 30°C. Upon reaction completion, the layers were separated, and the organic layer was concentrated. The residue was sequentially washed with 5 wt% aqueous sodium carbonate (1.9 kg, 0.9 mol) and water (1.75 kg), and the crude product was obtained. The crude product was distilled under vacuum at 100°C to afford **3** (833 g, 96% purity, 81%, yield from **4**) as a yellow liquid. MS $[M - F]^+$ m/z calcd 310.0278, found 310.0272. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.6 Hz, 1H), 6.38 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.15, 130.05 (d, J = 9.4 Hz), 124.71 (q, J = 269.11 Hz), 123.74 (dd, J = 11.7, 5.8 Hz), 120.72 (qd, J = 283.2, 28.1 Hz), 117.83 (d, J = 1.9 Hz), 110.78 (qd, J = 30.1, 2.1 Hz), 110.79 (d, J = 21.1 Hz), 91.40 (dp, J = 197.8, 32.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -63.22, -76.24 (d, J = 7.6 Hz), -173.92 – -186.48 (m).

ASSOCIATED CONTENT

Supporting Information

NMR spectra of compounds (PDF)

X-ray analysis of broflanilide (PDF)

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