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ARTICLE

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Scale-Up Synthesis of a TRPV1 Antagonist Featuring a Facile Thiazolo[5,4-*d*]pyrimidine Formation

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Supporting Information

ABSTRACT: An efficient and practical synthesis of a TRPV1 inhibitor bearing a thiazolo[5,4-*d*]pyrimidine core was developed. The initial synthesis was modified to facilitate acylation of 5-aminopyrimidine and subsequent thiazole formation. The synthesis features an efficient two-pot, five-step process for the construction of the thiazolo[5,4-*d*]pyrimidine ring. The new route is concise, chromatography-free, and amenable to large-scale preparation.

INTRODUCTION

The transient receptor potential vanilloid, subtype I (TRPV1 or VR1) receptor is the best characterized member of the transient receptor potential family of ion channels.[1] TRPV1 is believed to play an important role in transmitting inflammatory pain signals. It has become an attractive therapeutic target for the treatment of various neuroinflammatory disorders, and several small-molecule TRPV1 antagonists are currently in early clinical trials.[2] Our discovery team identified thiazolopyrimidine **1** (Figure 1) as an important lead compound.[3]

The key structural feature of **1** is the thiazolo[5,4-*d*]pyrimidine core, a close analogue of purine. This core is found in a variety of pharmacologically relevant molecules with potential indications for diabetes, cancer, and other diseases (**2**−**5**, Figure 2).[4−7] Examination of the syntheses of **2**−**5** shows that the assembly of 2-alkyl-thiazolo[5,4-*d*]pyrimidines is a nontrivial challenge. The syntheses typically involve thiolation/acylation of 5-aminopyrimidine followed by intramolecular ring closure. Unfortunately, these steps often require very harsh conditions and the use of highly malodorous reagents and suffer from unsatisfactory yields (5%, 10%, and 24% yield over two steps for **2**[4], **3**[5], and **4**[6], respectively). Here we report the development of an efficient and scalable synthesis of thiazolopyrimidine **1**.

RESULTS AND DISCUSSION

Initial Synthesis. The first synthesis of compound **1** was developed by our medicinal chemistry colleagues (Scheme 1).[3] Commercially available phenylacetic acid **6** was treated with thionyl chloride to give acid chloride **7**. Acylation of 5-amino-4,6-dichloropyrimidine (**8**) by **7** afforded amide **9**, which then underwent thiolation and intramolecular cyclization to provide thiazolopyrimidine **10**. After chlorination by $POCl_3$, the resulting chloropyrimidine **11** reacted with aniline **12** to give final product **1**. This synthesis was successfully completed on 10-g scale.

We analyzed the initial synthesis in Scheme 1 from a process chemistry perspective and identified two potential issues. First, the acylation of 5-aminopyrimidine **8** was very difficult. This is a common problem in the synthesis of thiazolo[5,4-*d*]pyrimidines and was a major cause for low yields in the preparation of **2** and **3** (Figure 2). In our case, the transformation could only be accomplished as a neat reaction at high temperature, which would pose safety hazards and operational difficulty on larger scale. Second, thiazole formation from **9** was accompanied by undesired hydrolysis of the chloropyrimidine functionality, which necessitated a subsequent rechlorination step. Product **11** was obtained in low overall yield after chromatographic purification. The process mass intensity (PMI)[8] value for the overall route was well over 1000, indicating significant adverse environmental impact if the process were to be adopted on large scale. It was clear that an improved route was highly desirable.

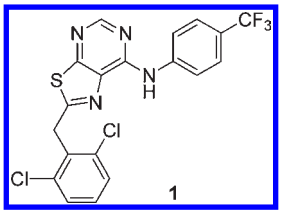

Figure 1. Structure of TRPV1 inhibitor **1**.

Route Scouting. We started by briefly investigating a different strategy that involved the coupling of thioamide **13** with various substituted pyrimidines (Table 1). Thioamide **13** was easily prepared in quantitative yield from commercially available 2,6-dichlorophenyl acetonitrile (**14**).[9] The coupling reaction was first tested with 5-amino-4,6-dichloropyrimidine (**8**) (entries 1−3). No reaction was observed under Pd-mediated coupling conditions. In the presence of acid or base after prolonged heating, nitrile **14** became the main product.[10] The coupling with aniline-substituted pyrimidine **15** gave similar results (entries 4−6). Finally, coupling with 4,5,6-trichloropyrimidine (**16**) was also examined but again failed to afford desired product (entries 7−8). The difficulty we encountered was in agreement

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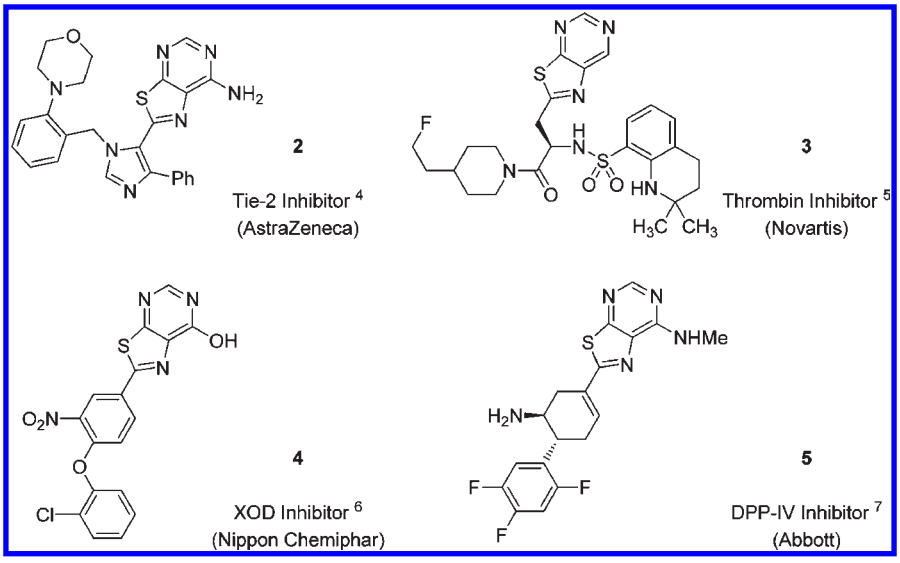
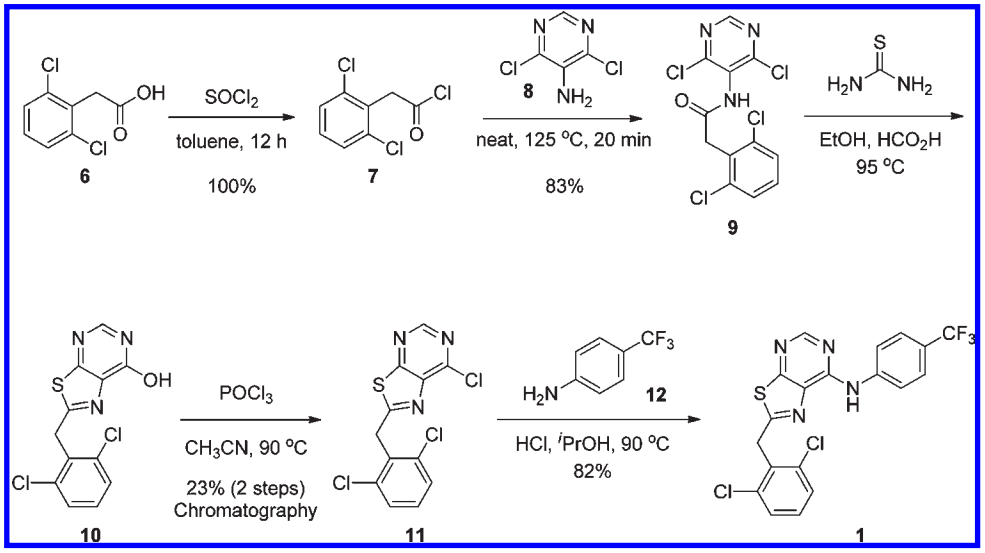


Figure 2. Several 2-alkyl-thiazolo[5,4-*d*]pyrimidines of clinical interest.

Scheme 1. Initial synthesis of 1



with the paucity of literature precedence for such transformations. Despite the prevalence of thiazole-fused heterocycles in the literature, formations of thiazoles via the coupling of thioamide and aromatic vicinal dihalides are rarely reported.[11]

We then turned our attention to the redesign of the original synthetic route. The difficult acylation of 5-aminopyrimidine **8** with acyl chloride **7** was first studied. Literature survey revealed that acylations of 5-aminopyrimidines are the most difficult when multiple electron-withdrawing substituents are present.[12] In the case of **8**, the 4,6-dichloro groups were the likely culprit for the sluggish acylation. We reasoned that if the aniline moiety was installed first to give **15** (Scheme 2), it should increase the electron density and facilitate acylation. Gratifyingly, the reaction between **15** and acyl chloride **7** in *N*,*N*-dimethylacetamide (DMA) was completed in only 1 h at room temperature, confirming that the reactivity was indeed significantly enhanced thanks to the electron-donating effect of the aniline substituent.[13]

Next, we examined the transformation of **17** to final product **1** via thiolation and intramolecular ring closure (Table 2). In the literature, similar sequences often suffer from unpleasant reagents, harsh conditions, and low yield. There are two possible pathways: electrophilic thiolation of the amide functionality to give thioamide **18**, or nucleophilic thiolation of chloropyrimidine to give thiopyrimidine **19**. Intramolecular cyclization of **18** or **19** then affords **1**. For electrophilic thiolation, P_2S_5[4,14] and Lawesson's reagent[6,15] are commonly employed. Indeed, reaction of **17** with Lawesson's reagent gave final product **1** directly (entry 1). However, the strong stench and moisture sensitivity of Lawesson's reagent are potential problems on large scale. On the other hand, nucleophilic thiolations of chloropyrimidines in the literature utilize either alkali sulfides[16] or thiourea,[17] the latter clearly the reagent of choice on large scale. We were pleased to find that reaction of **17** with thiourea gave **19** in moderate yield (entry 3). For the subsequent intramolecular cyclization step, we

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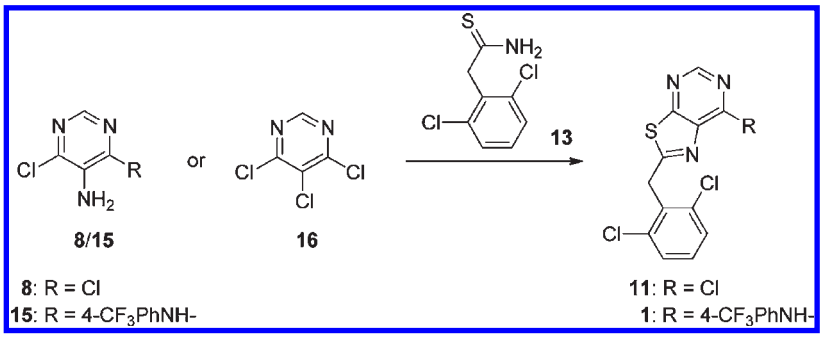
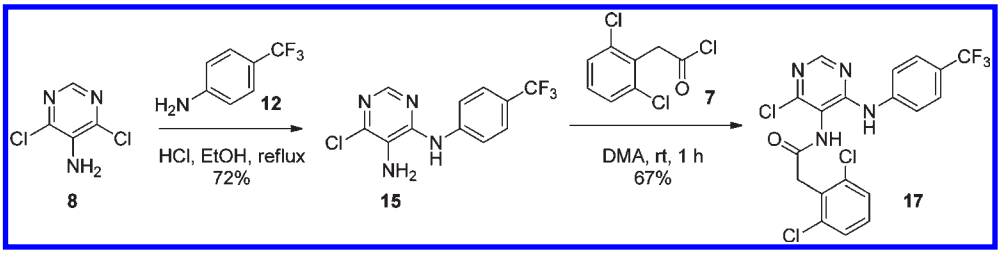
Table 1. Thiazole formation with thioamide 13



Entry	Reactant	Conditions	Results
1	**8**	HCl, IPA, 70 °C	**14**
2	**8**	K_2CO_3, DMF, 80 °C	**14**
3	**8**	$Pd(PPh_3)_4$, KO^{t}Bu, DMF, 100 °C	NR
4	**15**	K_2CO_3, DMF, 130 °C	Decomp.
5	**15**	$Cu(OTf)_2$, CH_3CN, 100 °C,	NR
6	**15**	$Pd_2(dba)_3$, dppf, KO^{t}Bu, DMF, 70 °C	**14**
7	**16**	Et_3N, DMA, 60 °C	Decomp.
8	**16**	Cu(I) thiophene-2-carboxylate, DMA, 60 °C	Decomp.

14

Scheme 2. Acylation of pyrimidine 15



screened both basic and acidic conditions[18] and found the reaction took place in the presence of excess HCl to afford **1** (entry 5).

Thus, an improved synthetic route was developed for the preparation of thiazolopyrimidine **1** (Scheme 3). The acylation of aminopyrimidine **8** was greatly facilitated by prior installation of the aniline moiety. The feasibility of subsequent thiolation and cyclization was also demonstrated. Compared to the original synthesis, the overall yield increased from 15% to 28%. The new synthesis also had a much lower PMI value of 188, a reduction of over 80%. Most importantly, this route served as a good starting point for further optimization and scale-up synthesis.

Route Optimization. To adapt the preliminary route for large-scale synthesis, several problems needed to be solved. The yields for acylation and thiolation were still relatively low. Several intermediates such as **17** and **19** have very poor solubility in most solvents, rendering the corresponding reactions highly heterogeneous and difficult to handle on large scale. Facile isolation and purification protocols also needed to be established. Finally, we believed if conditions were chosen strategically, it might be possible to combine two or more steps into a single reaction/operation and increase the overall efficiency.

We first examined the aniline substitution reaction and screened solvents, equivalents of reagents, and concentration.[19] The crude product **15** that precipitated out was collected and analyzed for yield and purity. The results showed that EtOH was the best solvent and that only a catalytic amount of HCl was needed. A slight excess of aniline **12** (1.1 equiv) was important to ensure complete consumption of pyrimidine **8** and higher yield of **15**. It is worth noting that no 4,6-disubstituted aniline was observed in the crude product of any reaction.[13] Finally, reactions at higher concentrations gave more solid precipitate, but at 2.0 M the crude product was contaminated with the HCl salt of aniline **12**. For the synthesis on larger scale, we decided to use HCl salt of aniline **12**, because it is a stable solid that can be easily stored and handled, and the commercial supply has higher purity. We were pleased to find that the yield increased to 76% on 140-g scale.[20]

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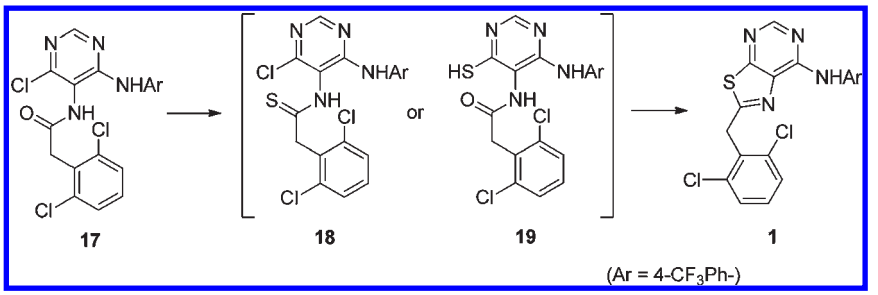
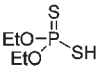
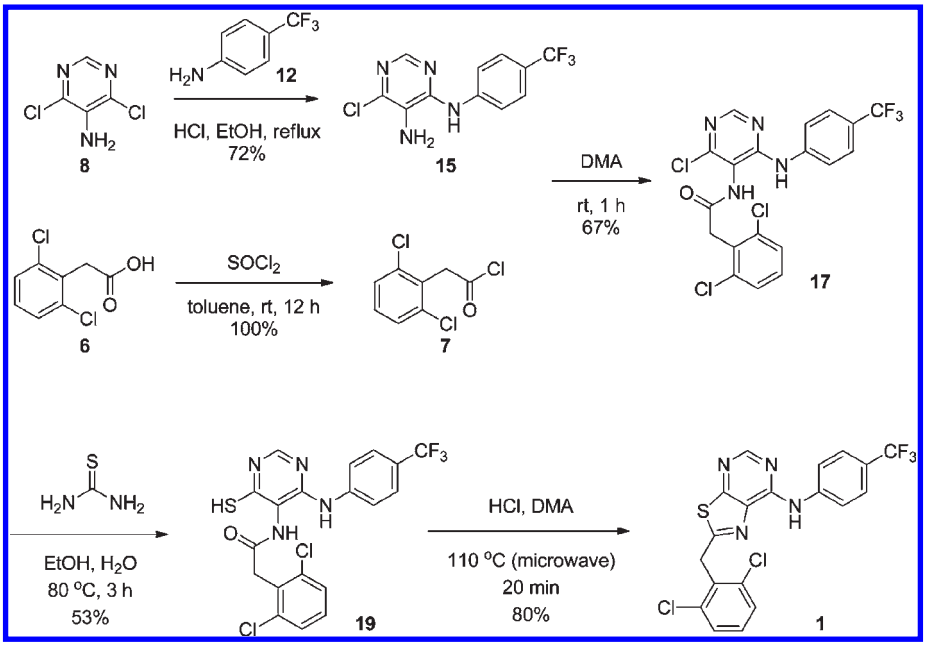
Table 2. Thiolation and cyclization



Entry	Reactant	Reagent	Conditions	Results
1	**17**	Lawesson's Reagent	Dioxane, 120 °C, 20 min[a]	**1** (70%)
2	**17**		H_2O, DMA, 80 °C, 20 min	NR
3	**17**	Thiourea	EtOH, H_2O, 80 °C, 3 h	**19** (53%)
4	**19**	None	DBU, DMA, 120 °C, 20 min[a]	NR
5	**19**	None	HCl, DMA, 110 °C, 20 min[a]	**1** (80%)

[a] Under microwave irradiation.

Scheme 3. Modified synthetic route



The next step was formation of acid chloride **7** from acid **6** (Scheme 4). Both thionyl chloride and oxalyl chloride could be successfully employed. Oxalyl chloride led to a faster reaction but also more off-gassing and a more substantial exotherm. In both cases, the reaction rate was significantly enhanced by the addition of a small amount of DMF.

The crude acid chloride formed was directly used as a solution in toluene in the subsequent acylation reaction. We found that complete acylation could be accomplished in CH_2Cl_2, CH_3CN, or DMA solvent with no need for a base or catalyst. However, both starting material **15** and product **17** were sparingly soluble in CH_2Cl_2 and CH_3CN, leading to sluggish reactions and highly heterogeneous reaction mixtures that would be difficult to handle on large scale. In contrast, the reaction in DMA was much more facile and remained homogeneous throughout. Product **17** was easily isolated by filtration upon addition of EtOH.

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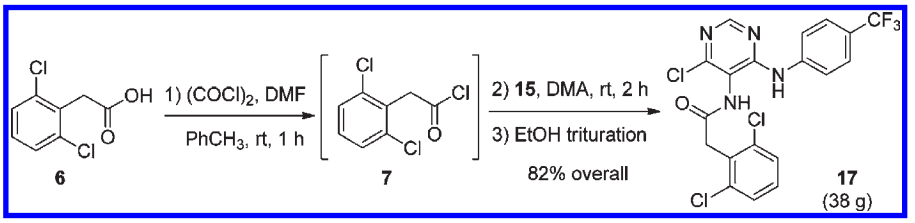
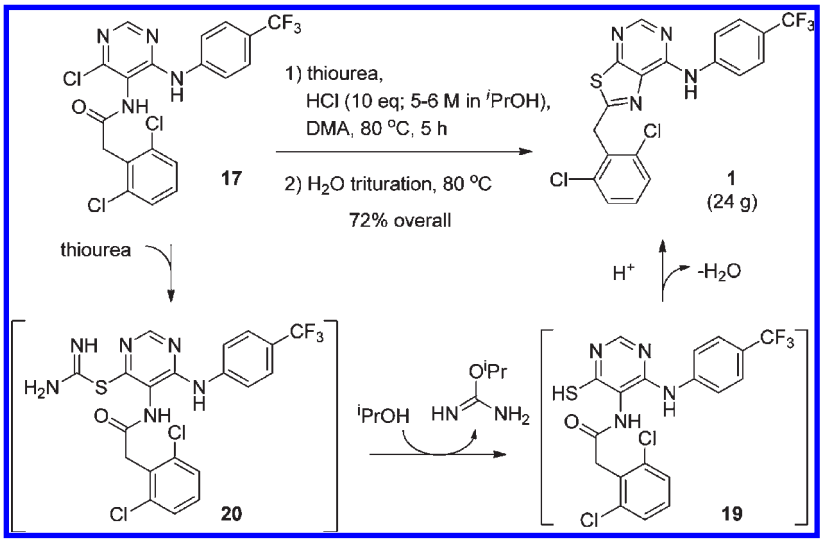
Scheme 4. Acylation of 5-aminopyrimidine 17



Scheme 5. One-pot thiazole formation



With compound **17** in hand, the thiolation/cyclization sequence was then studied. The thiolation step (thiourea, H_2O, EtOH, 80 °C) gave only moderate yield, in part due to the extremely poor solubility of starting material **17**, intermediate **19**, and product **1** in EtOH. Once again, this problem was solved by using DMA as solvent. It completely solublized the starting material **17** and led to a much faster and cleaner reaction. In this step, a nucleophilic additive was required to release thiol **19** from initial thiourea adduct **20**. EtOH and 2-propanol were found to be more efficient than water. Finally, since we had already established that the ensuing cyclization could occur in DMA under acidic conditions, the two steps were successfully combined. Thus, pyrimidine **17** was dissolved in DMA and treated with thiourea and HCl/2-propanol at 80 °C to directly give product **1** (Scheme 5). Commercially available 5−6 M HCl in 2-propanol was chosen to serve dual purposes: 2-propanol as the nucleophilic additive for the formation of thiol **19** from **20**, and HCl as the catalyst for the cyclization step.

Taking advantage of the fact that all solvents and byproducts (DMA, 2-propanol, HCl, and isopropyl carbamimidate) were water soluble, we developed a simple procedure to isolate product **1** by water trituration. Upon reaction completion, water was slowly added at 80 °C, and the resulting suspension was slowly cooled to give product **1** as a crystalline precipitate. Performing the trituration at elevated temperature and maintaining controlled slow cooling were found to be very important for achieving an acceptable filtration speed on large scale.

Crude product **1** from the above reaction contained residual solvents and small amounts of impurities including thiol **19** (~1.3 wt %). Solubility screening showed that **1** was sparingly soluble in alcohol but more soluble in EtOAc, ^{i}PrOAc, and acetone. Under the optimized final purification protocol, crude **1** was dissolved in hot acetone and filtered to remove thiol impurity **19**. The filtrate was heated to reflux again and triturated with water to afford pure **1** as a highly crystalline solid. Once again, performing trituration at elevated temperature and slow cooling were key to obtaining an acceptable rate of filtration. Using this route, the first batch of API **1** was prepared on 20-g scale. Compared to the preliminary synthesis (Scheme 2), the number of steps/operations was reduced, and the overall yield based on acid **6** was increased from 28% to 59%. The PMI value was again lowered to 77, a 60% reduction.

For the synthesis of the second and larger batch, we identified an interesting opportunity to further streamline the synthesis. Since acylation, thiolation, and cyclization all used DMA as solvent, we speculated that it might be possible to combine them into a one-pot operation. Gratifyingly, this was accomplished after optimization (Scheme 6). Thus, acyl chloride **7** was prepared from acid **6** and the reaction mixture in toluene was directly added to a solution of pyrimidine **15** in DMA. After complete acylation, thiourea and HCl/2-propanol were added, and the reaction was heated to 80 °C to give **1**. Once again, using DMA as the main solvent allowed the product to be easily isolated via water trituration. Overall, acid chloride formation, acylation, thiourea addition, thiol formation, and cyclization occurred sequentially in this easy two-pot operation to generate final product **1** from commercially available starting material **6**.

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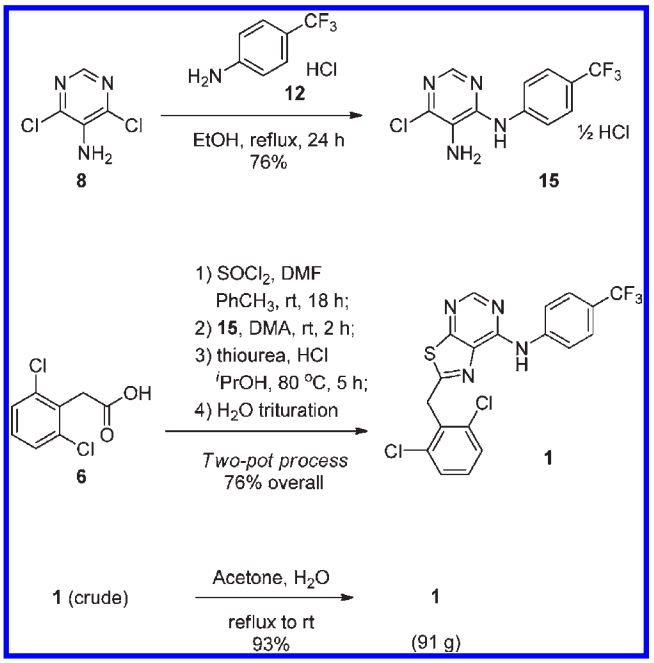
Scheme 6. Scale-Up Synthesis of 1



All four intermediates **7**, **17**, **20**, and **19** could be monitored by HPLC, which enabled convenient and precise in-process control. This new protocol not only increased operational efficiency but also enhanced overall yield from 59% to 76%. The optimizations further reduced the PMI value by another 40% to 44. The second batch of API was prepared on 90-g scale and used to support several pharmacokinetic and toxicology studies.

CONCLUSION

In summary, a scalable and concise synthesis of TRPV1 antagonist **1** was developed (Scheme 6). A key element in the route design was the installation of the electron-donating aniline moiety in the first step to facilitate acylation and thiazole formation. The initial route was then optimized to accommodate intermediates with limited solubility, allow expedient product isolation, and enable telescoping processes. The final synthesis featured an efficient two-pot, five-step process for the construction of the thiazolo[5,4-*d*]pyrimidine ring. The optimization greatly reduced adverse environmental impact, as evidenced by a 95% reduction in PMI value. These results should not only facilitate future preparation of **1** on larger scale, but also be of value to syntheses of other biologically active compounds bearing a similar thiazolopyrimidine core.

EXPERIMENTAL SECTION

General Methods. Toluene, CH_3CN, DMF, CH_2Cl_2, MeOH, and *N*,*N*-dimethylacetamide (DMA) were dried via passage through two alumina columns. All reactions were monitored by HPLC (Hewlett-Packard; Zorbax Eclipse XDB-C18, 5 μm, 4.6 mm × 150 mm column; gradient used: CH_3CN in H_2O, 5%−99% 5.0 min, 99% 1.0 min, 99%−5% 12 s, 5% 1.0 min; flow rate 2.0 mL/min; 35 °C).

6-Chloro-N^4-(4-trifluoromethyl-phenyl)pyrimidine-4,5-diamine (15). 5-Amino-4,6-dichloropyrimidine (**8**, 100 g, 0.61 mol, 1.00 equiv), ethanol (500 mL), and 4-aminobenzotrifluoride hydrochloride (**12**·HCl, 120 g, 0.61 mol, 1.00 equiv) was stirred at reflux temperature for 24 h and slowly cooled to room temperature. The resulting precipitate was collected by filtration, washed with ethanol (250 mL), and dried in a vacuum oven at 80 °C for 4 d to give **15** as a light-pink solid (141 g, 76%). ^{1}H NMR (600 MHz, d_6-DMSO, δ): 9.34 (s, 1H), 8.03 (d, J = 8.5 Hz, 2H), 7.96 (s, 1H), 7.68 (d, J = 8.6 Hz, 2H), 6.59 (br s, 3H); ^{13}C NMR (151 MHz, d_6-DMSO, δ): 148.0, 144.1, 143.6, 138.7, 125.7, 125.7 (q, J = 4.0 Hz), 124.5 (q, J = 271.4 Hz), 122.1 (q, J = 34.2 Hz), 119.8; MS (ESI$^+$): calculated for $C_{11}H_9ClF_3N_4$ [M + H$^+$], 289.0; m/z found, 289.0; HPLC retention time: 4.383 min. Based on elemental analysis results, the compound existed as a ~1:1 mixture of free base and HCl salt. Anal. Calculated for $C_{11}H_{8.5}Cl_{1.5}F_3N_4$: C, 43.05; H, 2.79; N, 18.26; Cl, 17.33; found: C, 43.31; H, 2.31; N, 18.31; Cl, 17.07.

2-(2,6-Dichlorobenzyl)-*N*-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*d*]pyrimidin-7-amine (1). 2,6-Dichlorophenylacetic acid (**6**, 62.5 g, 0.305 mol, 1.17 equiv) and DMF (1.60 mL) were dissolved in toluene (160 mL). Thionyl chloride (26.6 mL, 0.36 mol, 1.38 equiv) was added slowly over 10 min. The reaction mixture was stirred at 20 °C for 18 h, then added over 1.5 h to a solution of 6-chloro-N^4-(4-trifluoromethyl-phenyl)pyrimidine-4,5-diamine hemihydrochloride (**15**, 80.0 g, 0.261 mol, 1.00 equiv) in DMA (80 mL). The reaction was stirred at 20 °C for 2 h. Thiourea (31.6 g, 0.416 mol, 1.60 equiv) was added in one batch, followed by HCl in 2-propanol (5−6 M, 504 mL, ~2.77 mol, ~10.6 equiv) over 1 h via an addition funnel. The resulting solution was heated to 80 °C for 4 h. Water (340 mL) was added over 20 min and the resulting suspension was cooled to room temperature. The precipitate was collected by filtration and washed with ethanol (500 mL) to afford crude **1** (90 g, 76%) as a light-pink solid.

Final Purification of 1. A suspension of crude 2-(2,6-dichlorobenzyl)-*N*-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*d*]pyrimidin-7-amine (**1**, 98.0 g, 0.215 mol) in acetone (1.55 L) was heated to reflux and filtered. The filtrate was heated to reflux again. Water (620 mL) was added over 5 min, and the suspension was cooled to 20 °C over 4 h. The solid was collected by filtration and dried in a vacuum oven at 50 °C overnight to give **1** as a white crystalline solid (91.5 g, 93% yield). ^{1}H NMR (400 MHz, d_6-DMSO, δ): 10.43 (s, 1H), 8.58 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 8.1 Hz, 1H), 4.83 (s, 2H); ^{13}C NMR (126 MHz, d_6-DMSO, δ): 165.7, 162.8, 153.5, 152.4, 142.7, 135.4, 132.4, 130.8, 130.8, 128.9, 125.6 (q, J = 3.7 Hz), 124.4 (q, J = 271.2 Hz), 123.0 (q, J = 37.0 Hz), 121.1, 36.0; MS (ESI$^+$): calculated for $C_{19}H_{12}Cl_2F_3N_4S$ [M + H]$^+$, 455.0; m/z found, 455.1; HPLC retention time: 6.076 min; Anal. Calculated for $C_{19}H_{11}Cl_2F_3N_4S$: C, 50.12; H, 2.44; N, 12.31; found: C, 49.92; H, 2.27; N, 12.23.

ASSOCIATED CONTENT

Supporting Information. Optimizations for the synthesis of **15**; ^{1}H NMR and ^{13}C NMR spectra for compounds **15** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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(8) Process Mass Intensity (PMI) is defined as the total mass of raw materials input divided by the mass of final Active Pharmaceutical Ingredient (API) output. It is adopted by the ACS Green Chemistry Institute as one of the benchmarks to measure the environmental impact and sustainability of chemical processes. For a review of PMI and other similar benchmarks, see: Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

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(19) See Supporting Information for more details.

(20) The isolated product was found to contain ~0.5 equiv of HCl based on elemental analysis. See Experimental Section for details.