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An Efficient Synthesis of a Potent PPARpan Agonist

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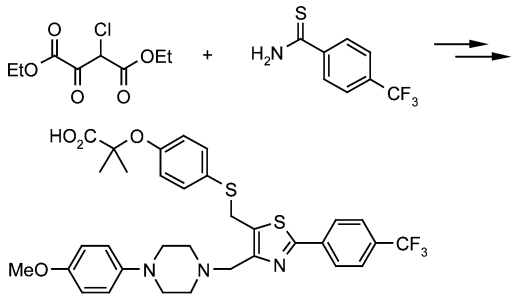

An efficient synthesis of 2-{4-[({4-{[4-(4-methoxyphenyl)-piperazin-1-yl]methyl}-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)thio]phenoxy}-2-methylpropanoic acid (**1**), a potent PPARpan agonist, is described. The seven-step synthesis, which afforded **1** in 30% overall yield, includes a highly regioselective carbon−sulfur bond formation via coupling of a bishydroxymethylthiazole (**3**) with 4-hydroxythiophenol, displacement of the remaining alcohol through a three-step telescoped sequence involving an efficient cleavage of an aryl mesylate, and an efficient and practical method of introducing an isobutyric acid fragment.

Peroxisome proliferator-activated receptors (PPARs) are ligand-sensitive nuclear factors with three subtypes: PPARα, PPARγ, and PPARδ. PPARs play an important role in many cellular functions and have emerged as therapeutic targets for the treatment of human metabolic diseases.[1−6] To address multiple metabolic disorders more effectively, the simultaneous activation of PPARα, PPARγ, and PPARδ by a single compound (i.e., a PPARpan agonist) is being pursued. Furthermore, the simultaneous activation of individual PPARs with a single pan molecule may result in synergistic effects, affording enhanced biological activity and increased potency.[6] On the basis of preclinical data, compound **1** was identified as a potent PPARpan agonist.[7] The original synthesis of **1** (Scheme 1), not designed for atom efficiency or waste minimization, involved 14 linear steps and was not amenable for large-scale preparation due to many safety and scalability issues within the synthesis.[7]

To provide sufficient quantities of **1** for preclinical and clinical studies, an efficient, practical, and scalable route was required. As shown in the retrosynthetic analysis depicted in Scheme 2, we envisioned that a regioselective carbon−sulfur bond formation could be achieved directly from the diol **3** and the thiophenol **2** under acidic conditions.[8] We predicted that a stable carbocation would be generated preferably at the C-5 hydroxymethyl of the thiazole ring in diol **3**.[9] Thus, an S_N1 displacement should be more favored at the C-5 hydroxymethyl group,[10] leading to a very efficient synthesis of **1**.

In this paper, we report an efficient and practical synthesis of **1** in 7 steps with 30% overall yield.

The synthesis of **1** began with condensation of commercially available diethyl 2-chloro-3-oxosuccinate (**4**) with 4-(trifluoromethyl)thiobenzamide (**5**) in ethanol, which afforded the diester **6** in 83% yield (Scheme 3).

Reduction of **6** with LAH yielded diol **3**. To avoid undesired mono- and bisdesfluoro byproducts (**7** and **8**), which carried through to **1** as major impurities, the reaction temperature was maintained below −10 °C. Thus the reduction was carried out at −10 to −15 °C in THF followed by acid workup with aqueous sulfuric acid, affording **3** in 83% yield without the formation of the desfluoro side products.

We next turned our attention to the regioselective carbon−sulfur bond formation at the C-5 hydroxymethyl. We explored two approaches to form the carbon−sulfur bond: synthesis of the thiophenol **2** and in situ coupling with **3**; direct coupling of **3** with commercially available 4-hydroxythiophenol. To pursue

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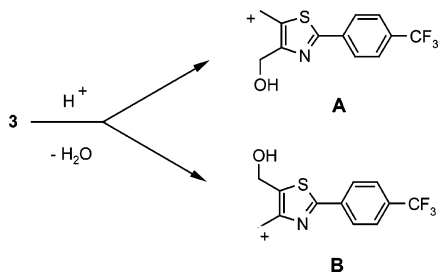
(9) Under acidic conditions, **3** may form carbocations at two positions, C-5 hydroxymethyl carbon (carbocation A) or C-4 hydroxymethyl carbon (carbocation B). The carbocation A has greater stability because of the increased delocalization due to resonance (7 canonical forms) within the thiazole and the benzene rings, while the carbocation B (3 canonical forms) is stabilized only by delocalization with a 4,5-double bond and the mercapto atom.



(10) On the basis of MOPAC/PM3 calculations, it was found that the carbocation A is 11 kcal/mol lower in energy than that of the carbocation B. This result indicates that the primary product should be the expected one.

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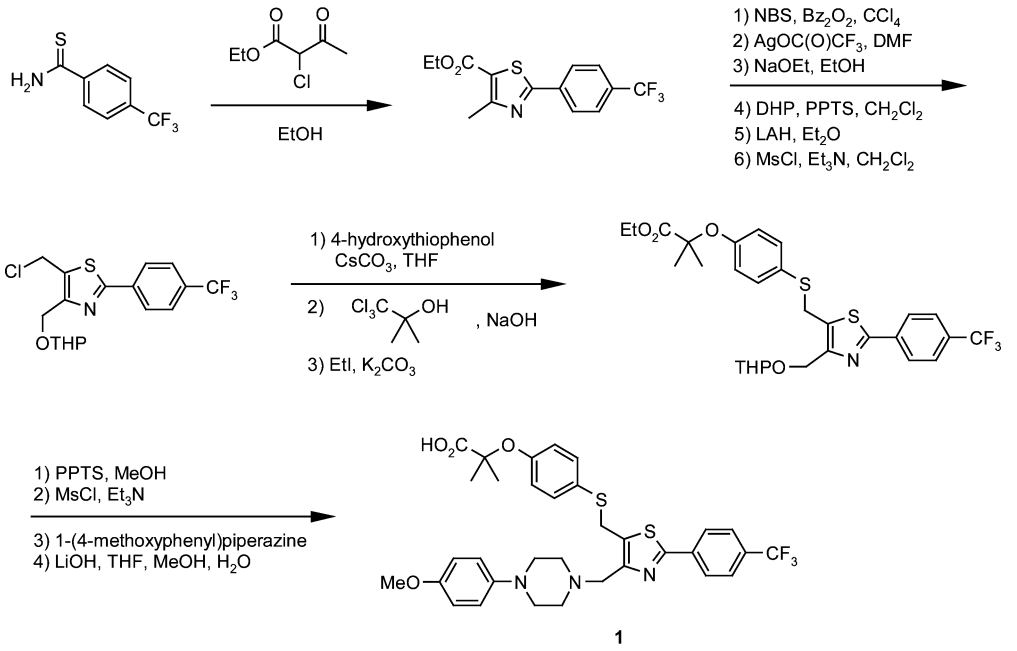
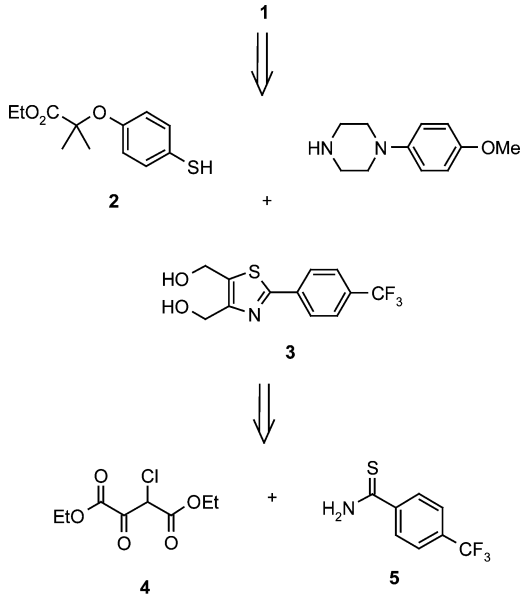
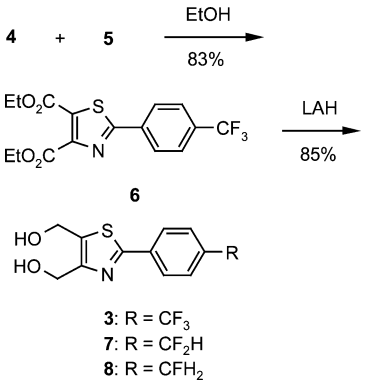
SCHEME 1



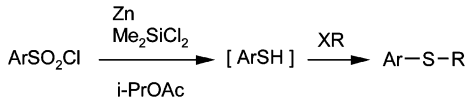
SCHEME 2



SCHEME 3



SCHEME 4



the former approach, it was necessary to prepare the required O-substituted thiophenol **2**. It had been reported[11] that aromatic sulfonyl chlorides are reduced to aromatic thiophenols with Zn/Me_2SiCl_2 in dichloroethane, in the presence of DMA (*N*,*N*-dimethylacetamide) or DMF. DMA and DMF are reported to serve as activating agents, converting sulfonyl chlorides to Vilsmeyer-type reactive iminium salts. Further, it was reported that, in the absence of DMA or DMF, no reaction had taken place. In our efforts to replace 1,2-dichloroethane with a more desirable solvent for large-scale preparation, we identified isopropyl acetate. Further, we found that reduction of the sulfonyl chlorides in isopropyl acetate did not require DMA or DMF as additives and allowed in situ coupling to be achieved in a single pot, giving thioether products while minimizing potential disulfide formation (Scheme 4).[12]

Although these conditions provided a convenient single-pot process, the reduction was found to be very exothermic under anhydrous conditions, and the exotherm was not addition controlled. An induction period followed by an extremely large and sudden exotherm was observed even when only small amounts of Me_2SiCl_2 had been added.[13] However, the presence of a small amount of residual water in the sulfonyl chloride moderated the exotherm, and by slow addition of Me_2SiCl_2 to a mixture of the sulfonyl chloride and zinc dust in isopropyl acetate, the reaction proceeded smoothly under addition control with only a mild, addition-controlled exotherm. The reduction of the sulfonyl chloride to the thiophenol was typically complete

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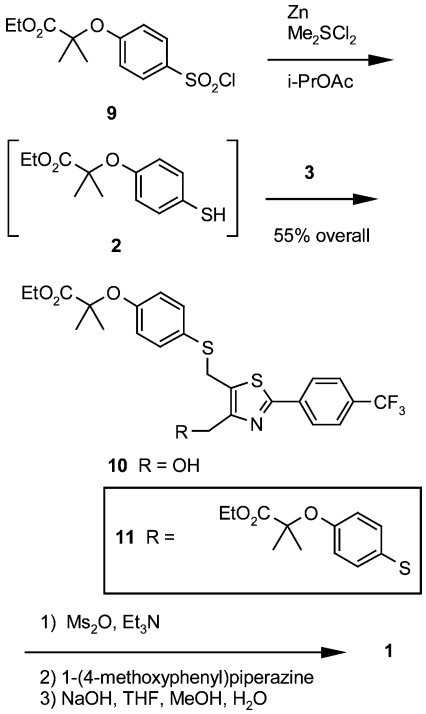
(13) The sulfonyl chloride was reduced to a sulfinic acid after the initial vigorous exotherm.

SCHEME 5



on conclusion of the Me_2SiCl_2 addition. The exotherm could be further reduced by adding a mixture of a sulfonyl chloride and Me_2SiCl_2 (0.25−0.75 equiv) in isopropyl acetate to a suspension of zinc dust in isopropyl acetate containing small amounts of water (0.5 equiv). In these reactions, Me_2SiCl_2 first reacts with water to form HCl and polysiloxane. The sulfonyl chloride is reduced by Zn/HCl to a sulfinic acid, which subsequently is reduced by Zn/Me_2SiCl_2 to thiophenol under anhydrous conditions. Alternatively, a mild reduction can be achieved via a single-pot process by reducing sulfonyl chlorides to sulfinic acids with $Zn/HOAc/H_2O$ followed by reduction of the sulfinic acids to thiols with Zn/Me_2SiCl_2.[12]

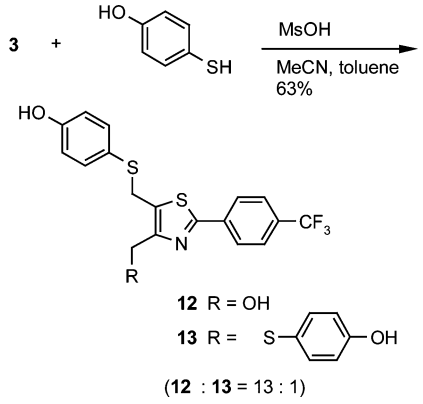
Using the reaction conditions described above, the sulfonyl chloride **9**[7] was reduced with Zn/Me_2SiCl_2 in isopropyl acetate to the thiophenol **2**, which was then coupled in situ with **3**, affording the desired coupling product **10** with excellent regioselectivity (Scheme 5).

Of the two potential side products, the bis-coupling product **11** and C-4 regioisomer, only the bis-coupling product, **11**, was produced, and in small amounts. This impurity was removed by crystallization from EtOH/isooctane (1:1), giving the desired product **10** in 55% isolated yield with 98% purity. The mono-coupling regioisomer at the C-4 hydroxymethyl carbon was not detected at all.

Mesylation of the hydroxymethyl in **10**, followed by displacement of the primary mesylate with 1-(4-methoxyphenyl)-piperazine and saponification of the ester with aqueous sodium hydroxide, afforded **1**. The efficiency of the process was successfully demonstrated on a 50 L scale, producing several batches of **1** (up to 2 kg per batch).

Having established regioselective control and crystallization methods for rejection of bisalkylated products, an alternative and more efficient preparation was accomplished via direct coupling of **3** with 4-hydroxythiophenol. The coupling of **3** with 4-hydroxythiophenol in MeCN/toluene in the presence of methanesulfonic acid was achieved with excellent regioselectivity, affording **12** in 63% isolated yield with 98% purity (Scheme 6).

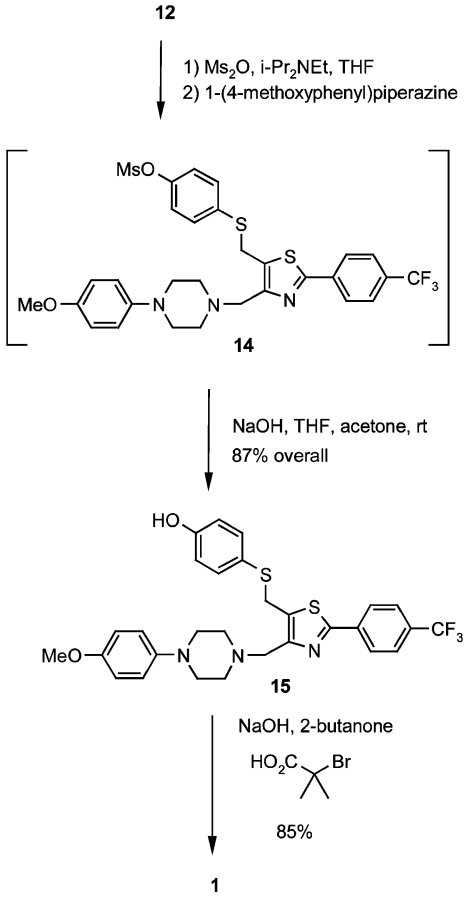
SCHEME 6



Again, the undesired mono-coupling product at C-4 hydroxymethyl was not detected, while the bis-coupling side product **13** (approximately 1:13 vs the desired product) was removed during crystallization. To assemble the piperazine fragment, the hydroxymethyl group in **12** needed to be converted to an active leaving group. Treatment of **12** with methanesulfonic anhydride and Hunig's base in dichloromethane thus gave a bismesylate (Scheme 7).

Use of methanesulfonic anhydride as the mesylating agent was found to be essential since treatment of **12** with methanesulfonyl chloride resulted in the corresponding alkyl chloride.

SCHEME 7



The chloride was found to be a poor substrate for subsequent displacement with the piperazine. The alkyl mesylate, on the other hand, was readily displaced with 1-(4-methoxyphenyl)-piperazine, while the aryl mesylate served as a protecting group for the phenol. Although the use of sulfonates as protecting groups for phenols has recently attracted more attention,[14,15] removal of an aryl mesylate or aryl tosylate often requires vigorous conditions.[15,16] However, our research indicated that aryl mesylate **14** could be readily cleaved by treatment with 20−40 mesh NaOH beads in acetone or THF/acetone containing small amounts (1−2 equiv) of water at room temperature. The reaction is heterogeneous. The added water probably increases the solubility of NaOH in the reaction medium thus increasing the nucleophilicity of the hydroxide anion and consequently the reaction rate. The reaction proceeded very slowly under anhydrous conditions. Use of 20−40 mesh NaOH beads was found to be necessary to achieve the mild and efficient cleavage of the aryl mesylate. The demesylation proceeded very slowly when other forms of NaOH, such as flakes, pellets, or aqueous solution, were used. Using the conditions described, demesylation of **14** was complete within 1 h and afforded phenol **15** in 87% isolated yield.

The final step of the route required assemblage of the 2-isobutyric acid fragment, which had previously been introduced via alkylation of **15** with ethyl 2-bromoisobutyrate and K_2CO_3 in ethanol followed by hydrolysis. However, ethyl methacrylate, which tends to polymerize under the reaction conditions, was obtained as a major side product. Polymethacrylate, although not an issue for small-scale synthesis, posed quality issues on scale. Additionally, polymer-coated vessels posed cleaning issues. Alternatively, the 2-isobutyric acid fragment was assembled via the Bargellini chemistry[17] (1,1,1-trichloro-2-methyl-2-propanol with NaOH). However, the exothermic nature of the reaction posed a safety issue[18] for large-scale preparation. To address these issues, we developed an efficient, controlled, and practical method using 2-bromoisobutyric acid as an alkylating agent to introduce the isobutyric acid moiety.[18] Thus, alkylation of **15** with 2-bromoisobutyric acid in 2-butanone furnished **1** in excellent yield, while avoiding the polymerization and safety problems. The purity of the final product **1** was consistently over 99%.

In summary, we have developed a highly efficient, practical, and scalable route for the synthesis of the potent PPARpan agonist **1**, with 30% overall yield, shortening the original synthesis from 14 linear steps to 7 steps. Acid-catalyzed coupling of the diol **3** with 4-hydroxythiophenol provides an efficient and highly regioselective means of forming the carbon−sulfur bond. To the best of our knowledge, there is no precedent in the literature for this kind of differentiation on the thiazole nucleus. A multistep sequence involving a mild deprotection of a phenol mesylate introduces the piperazine fragment efficiently. Finally, using 2-bromoisobutyric acid as the alkylating agent assembles the isobutyric acid moiety effectively and efficiently. The route is free of column chromatography and is amenable for large-scale preparation of **1**.

Acknowledgment. We thank Dr. Alan Millar for helpful comments and discussions.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for compounds **1**, **3**, **6**, **10**, **12**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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