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A facile method for converting alcohol to thioether and its application in the synthesis of a novel GPR119 agonist

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ABSTRACT

We studied a modified Mitsunobu reaction for the direct conversion of alcohol to thioether, resulting in a high yield and requiring fewer steps. A facile method for synthesizing a novel GPR119 agonist, (*R*)-1,1,1-trifluoropropan-2-yl-6-(4-(((pyridin-2-ylmethyl)sulfonyl)methyl)phenyl)spiro[chromane-2,4′-piperidine]-1′-carboxylate (**1**), was established starting from the key intermediate alcohol **3** to pyridylmethylthioether **14** by using $PPh_3(OCH_2CF_3)_2$ without protection of the piperidine moiety, resulting in an excellent yield. Finally, the efficient oxidation of the sulfide and carbamoylation of the piperidine moiety afforded the desired product **1**.

1. Introduction

G protein-coupled receptor 119 (GPR119) is predominantly expressed in pancreatic β-cells and incretin-releasing L-cells in the intestine. The activation of GPR119 increases the intracellular accumulation of cAMP, leading to enhanced glucose-dependent insulin secretion from pancreatic β-cells and increased release of gut peptides GLP-1 (glucagon-like peptide 1). Therefore, GPR119 agonists are expected to be promising targets for the treatment of type 2 diabetes with a low risk of hypoglycemia and obesity by improving glucose homeostasis.[1] Recently, we discovered that (*R*)-1,1,1-trifluoropropan-2-yl-6-(4-(((pyridin-2-ylmethyl)sulfonyl)methyl)-phenyl)spiro[chromane-2,4′-piperidine]-1′-carboxylate (**1**) was a highly potent GPR119 agonist (EC_{50}=54 nM) with a hypoglycemic effect (3 mg/kg po, 30% glucose AUC decrease) in OGTT/C57BL mice.[2] To move to the pre-clinical stage, we must develop an efficient synthetic method for providing a robust supply of **1**. Therefore, we recently established a practical method[3] for synthesizing key intermediate **3** starting from commercially available material **6** to avoid constructing the biphenyl framework using a palladium cross-coupling reaction between **4** and **5**; the development of this method involved some challenges, such as palladium scavenging, residual metal control, use of expensive materials and potential genotoxicity, as shown in Fig. 1.

Currently, our attention is focused on a divergent synthesis to efficiently provide a variety of screening samples[2] from stable benzyl thioacetate **8** as a common intermediate, as shown in Scheme 1. In a previous synthesis, benzyl alcohol **2** was brominated using a combination reagent consisting of triphenylphosphine and tetrabromomethane to afford benzyl bromide **7**, which was reacted with potassium thioacetate to yield **8**. The desired thioethers were obtained by reacting **8** with appropriate alkylating reagents under alkaline conditions.

Next, the prepared thioethers were converted to sulfones using a Na_2WO_4–H_2O_2 system under neutral conditions. After cleavage of the *N*-Boc group of piperidine, the appropriate carbamoylation afforded the desired products. Clearly, this synthetic route required

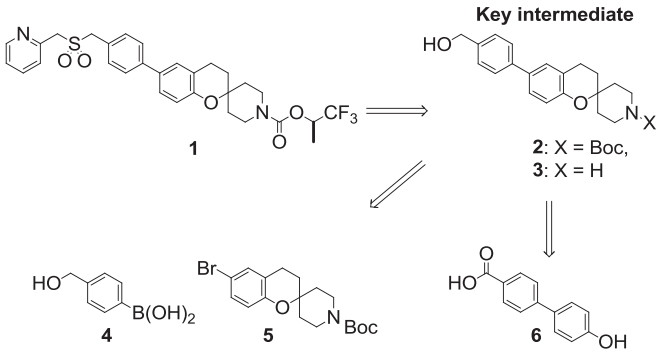

Fig. 1. Retrosynthetic analysis of **1**.

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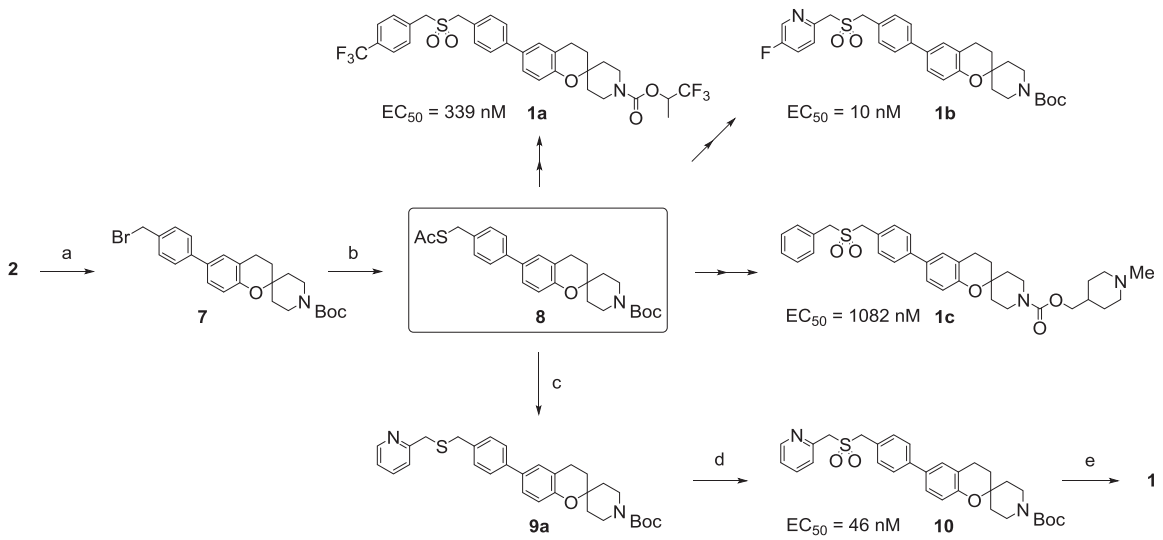

Scheme 1. Previously proposed route for the synthesis of divergent samples. Reagents and conditions: (a) PPh_3, CBr_4, CH_2Cl_2, rt, 93%; (b) KSAc, DMF, rt, 84%; (c) 2-bromomethyl)-pyridine hydrobromide, 6 N NaOH, MeOH, THF, rt, 75%; (d) H_2O_2, $Na_2WO_4{\cdot}2H_2O$, 2-propanol, 50 °C, 93%; (e) (i) 4 N HCl in AcOEt, CH_2Cl_2, rt; (ii) (*R*)-1,1,1-trifluoropropan-2-yl 1*H*-imidazole-1-carboxylate, *N*,*N*-diisopropylethylamine, DMF, 80 °C, 64% (2 steps).

several steps, including protection and de-protection procedures, and involved hazardous intermediate **7**.

2. Results/discussion

In pursuit of a practical approach, we developed an efficient synthetic method for the direct conversion of alcohol to thioether[4] without protection. Therefore, we investigated the redox condensation system of the Hata reaction[5] or Mitsunobu reaction[6] to treat alcohol with disulfides or thiols (Fig. 2).

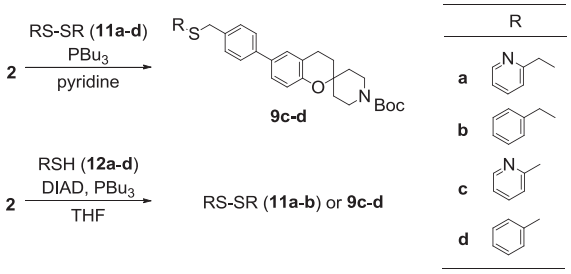

Fig. 2. Reaction of **2** with disulfides **11(a–d)** or thiols **12(a–d)** using Hata reaction or Mitsunobu reaction.

To explore the feasibility of this approach, we first attempted to conduct the Hata reaction between benzyl alcohol **2** and 1,2-bis(pyridin-2-ylmethyl) disulfide (**11a**),[7] which failed to produce thioether **9a**. Then, we investigated the reactivity of other disulfides; the results are summarized in Table 1. **9b** was not obtained, and 1,2-di(pyridin-2-yl) disulfide (**11c**) and 1,2-diphenyl disulfide (**11d**) afforded the corresponding thioethers **9c** and **9d** in 99% and 62% yields, respectively.

Table 1
Synthesis of thioethers **9** (**a**–**d**) from each disulfide **11** (**a**–**d**) via the Hata reaction

Entry	Disulfide **11**	Thioether **9**	Yield
1	**a**; 1,2-bis(pyridin-2-ylmethyl) disulfide	**9a**	n.r.[a]
2	**b**; 1,2-dibenzyl disulfide	**9b**	n.r.[a]
3	**c**; 1,2-di(pyridin-2-yl) disulfide	**9c**	99%
4	**d**; 1,2-diphenyl disulfide	**9d**	62%

[a] n.r.=no reaction.

Next, we investigated the reactivity of **2** in the Mitsunobu reaction with thiols **12** (**a**–**d**) using a combination of diisopropyl azodicarboxylate (DIAD) and tributylphosphine (PBu_3) in THF; the results are summarized in Table 2.

Table 2
Synthesis of thioethers **9** (**a**–**d**) from each thiol **12** (**a**–**d**) via the Mitsunobu reaction

Entry	Thiol **12**	p*Ka*	Thioether **9**	Yield
1	**a**; pyridin-2-ylmethanethiol	8.93[b]	**9a**	n.o.[a]
2	**b**; phenylmethanethiol	9.43[c]	**9b**	n.o.[a]
3	**c**; pyridin-2-thiol	−1.07[c]	**9c**	99%
4	**d**; benzenethiol	6.52[c]	**9d**	87%

[a] n.o.=not obtained.
[b] predicted value.[8]
[c] measured value.[9]

In both types of reactions, there is a difference in the chemical yields between entries 1–2 and entries 3–4. This result is due to pyridin-2-thiol (**12c**) and benzenethiol (**12d**) possessing a lower p*Ka* that is sufficient to protonate the hydrazine anion formed from DIAD, which promoted the formation of thioether rather than pyridin-2-ylmethanethiol[7] (**12a**) and phenylmethanethiol (**12b**). Interestingly, when monitoring the progress of a reaction with the TLC, disulfides **11** (**a**–**d**) were identified and observed to result in the oxidation of thiols **12** (**a**–**d**) in the Mitsunobu reaction. In fact, the disulfides[10] that were generated in situ from the thiols and DIAD were subsequently reacted with PBu_3 to form the thioalkoxide tributylphosphonium salt (**III**) followed by reaction with alcohol **2** to yield the alkoxide phosphonium intermediate (**IV**). This activating intermediate reacted with the stronger nucleophiles, such as the negative anions of **12c** and **12d**, along path a to yield **9c** and **9d**, respectively (entries 3 and 4, respectively). However, weak nucleophiles, such as **12a** and **12b**, competed with the hydrazine anion of DIAD along path b toward intermediate **IV** and resulted in the production of sub-product **13** in 52% and 64% yields, respectively. The plausible mechanism for this reaction series is shown in Scheme 2.

To suppress the production of **13**, we enhanced the nucleophilicity of **12a** in the presence of a base in the Mitsunobu reaction. The removal of the Boc group from **2** results in the production of piperidine **3** as a free base (p*Ka*=11.2),[11] which can abstract the acidic proton (p*Ka*=8.9) of thiol **12a**. We expected that the formed thiolate