COMMUNICATION

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BF_3•Et_2O Promoted Sulfuration of Steroidal Sapogenins

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A reaction between steroidal sapogenins and hydrogen sulfide promoted by BF_3•Et_2O is described. The thiodiosgenin and thiotigogenin comprising a sulfur atom on the F ring can be easily afforded in one step under this mild reaction condition. Furthermore, a hypothetical mechanism is also shown.

Keywords steroidal sapogenin, hydrogen sulfide, sulfuration, spiroketal, resource chemistry

Introduction

Steroidal sapogenins are well-known naturally found compounds which have been extensively used in the industrial synthesis of steroid drugs.[1] Interestingly, many saponins themselves also have various pharmacological activities, such as an antitumor activity, antibacterial activity, and anti-inflammatory activity.[2] The structure-activity relationships (SAR) study revealed that the activity of steroidal sapogenins largely depended on the stereochemistry and the hetero atoms of the E and F rings.[3] Thus, the efficient synthesis of solasodine and thiodiosgenin in which the oxygen atom is replaced by a nitrogen and sulfur atom, respectively, on the F ring is demanded (Figure 1). These resulting compounds are worthy for further bioactivity evaluation.

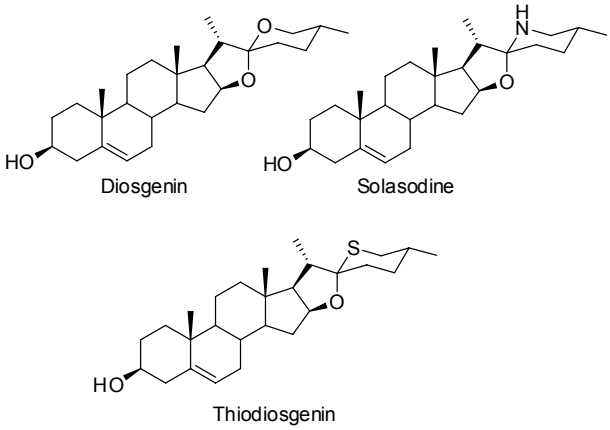

Figure 1 Structure of diosgenin, solasodine and thiodiosgenin.

In 1954, Uhle[4] reported the preparation of solasodine from pseudodiosgenin through the hydrolysis of 26-phthalimidopseudodiosgenin derived from 26-iodopseudodiosgenin. Later, the streamlined synthesis of thiodiosgenin from pseudodiosgenin in five steps via 26-thioacetyl-pseudodiosgenin was shown (Scheme 1).[5] In 2003, Saito and co-workers[6] showed the preparation of thiodiosgenin and selenodiosgenin bearing S atom and Se atom, respectively, on the F rings. This synthesis route was similar to Uhle's report, where the 26-iodopseudodiosgenin was the key intermediate. Recently, Li and Lou[7] also reported the synthesis of thiodiosgenin for further cytotoxicity study. In order to utilize the natural resource compounds in a more "atom economical" way, we started to investigate a more efficient and concise method for the synthesis of thiodiosgenin and thiotigogenin from steroidal sapogenin directly. It is known that the spiroketal ring system of steroidal sapogenin is usually stable to most reagents. However, the C-23-deuterium or bromine substitution,[8] Clemmensen reduction,[9] mercaptolysis,[10] and the isomerization of rings E/F[11] all indicated that they existed in an equilibrium between the spiroketal and its opened side-chain tautomer under acidic solution. Based on this cognition, we developed a BF_3•Et_2O-promoted sulfuration of steroidal sapogenin with hydrogen sulfide, giving the thiodiosgenin and thiotigogenin directly in one step under mild conditions.

Experimental

General procedure for the synthesis of thiodiosgenin

To a solution of diosgenin acetate **1** (2 mmol, 912 mg) in DCM (20 mL), BF_3•Et_2O (0.8 mL, 6 mmol) was added at 0 ℃. Hydrogen sulfide gas generated *in situ* from concentrated sodium sulfide solution and diluted sulfuric acid was slowly bubbled through the solution. The resulting reaction mixtures were stirred at 15 ℃.

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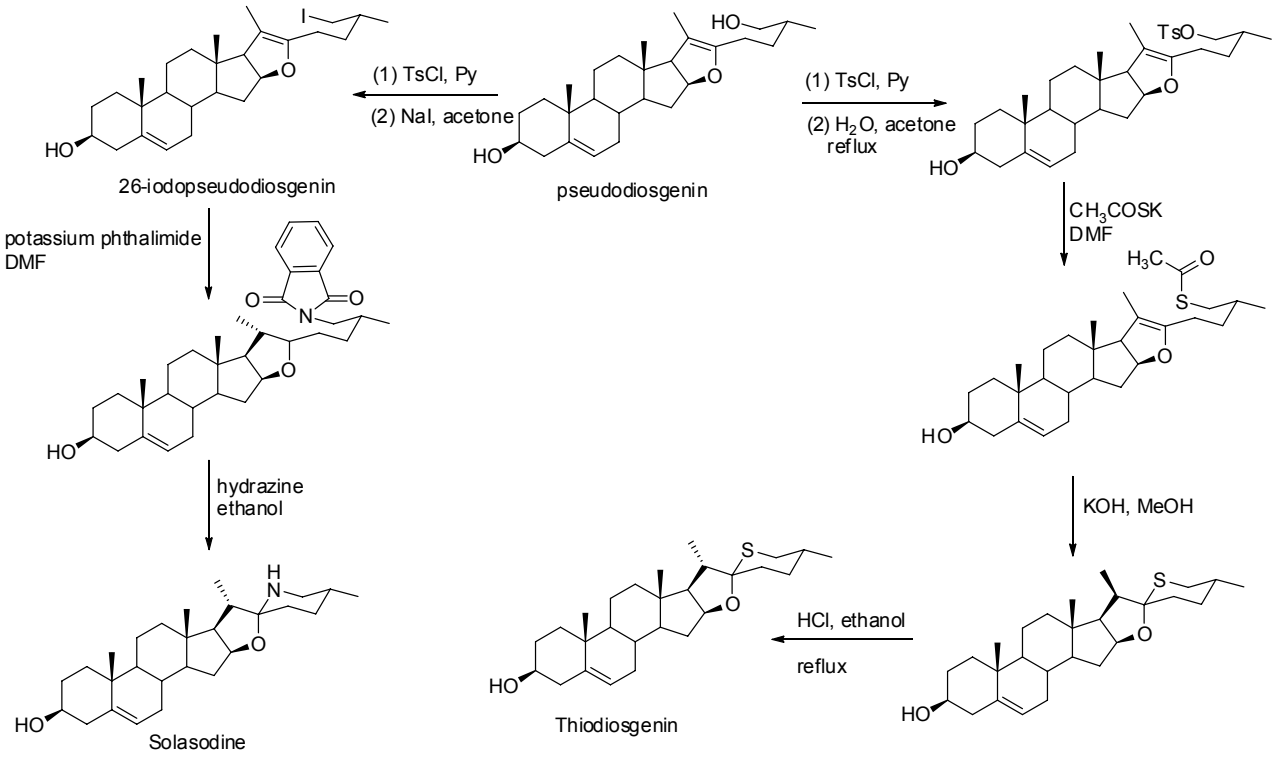
Scheme 1 Synthesis of solasodine and thiodiosgenin

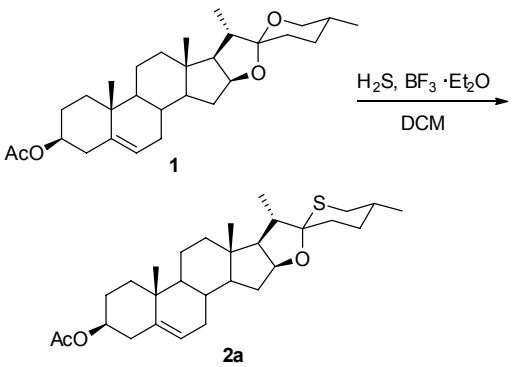


The reaction was followed by TLC until diosgenin was completely consumed. The reaction mixtures were allowed to reach room temperature and diluted with DCM (40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. The filtrate was evaporated under reduced pressure to afford the crude product. This crude oil was purified by flash chromatography to afford the product **2a** (462 mg) as a white solid in 51% yield.

Results and Discussion

Our previously study[10] indicated that the F spiroketal ring in diosgenin is always not stable in acidic solution. Thus, we alternatively surveyed several Lewis acids, such as $FeCl_3$, $ZnCl_2$, trifluoromethanesulfonic acid, and BF_3•Et_2O, for facilitating the reaction between diosgenin and H_2S. To our delight, BF_3•Et_2O could afford the expected thiodiosgenin at 10 ℃, though the yield was relatively low. Encouraged by the initial result, we began to further optimize the reaction conditions (Table 1). The reaction temperature played a significant role in this reaction. Increasing the reaction temperature from 10 to 15 ℃ led to 48% of **2a** (Entry 3). Further increasing the temperature to 20 ℃, the yield was dropped to 11%, and some undissolved polymeric residues were found (Entry 4). When the reaction was run at 25 ℃, only trace **2a** was detected (Entry 5). Lowering the reaction temperature to 0 ℃ resulted in a sluggish mixture (Entry 1). This reaction was found sensitive to concentration. When the reaction was carried out in 20 mL DCM, the yield of **2a** was slightly improved from 48% to 51% (Entry 6), yet 46% yield was obtained if the solvent volume was 30 mL (Entry 7).

Table 1 Optimization of reaction conditions for BF_3•Et_2O-promoted sulfuration of diosgenin acetate[a]



Entry	Solvent volume/mL	Temp./℃	Time/h	Yield[b]/%
1	10	0	16	＜5
2	10	10	8	39
3	10	15	4	48
4	10	20	2	11
5	10	25	2	Trace
6	20	15	5	51
7	30	15	6	46

[a] All reactions were carried out under N_2 atmosphere, **1** (1.0 equiv.), BF_3•Et_2O (3 equiv.) in DCM. [b] Isolated yield. DCE＝1,2-dichloroethane.

Moderate yield of thiodiosgenin acetate **2a** was ob-

tained even under optimal condition because some polymer products were formed during the course of this reaction. Among them, two main side products **2b** and **2c** were obtained in 16% and 11% yield, respectively (Figure 2).

Having identified the expected product and side products, a plausible mechanism for this BF_3•Et_2O-promoted sulfuration of diosgenin acetate is proposed (Scheme 2). The acid-catalyzed isomerization of **1** to intermediate **B** proceeds by a redox pathway, which was previously proposed by Woodward.[12] The aldehyde **B** is attacked by H_2S to form acetal **C**, which gives thioaldehyde **D** after losing a molecule of H_2O. Intermediate **E** results from subsequent redox reaction, then **E** further cyclizes to the product **2a** ((3*α*,20*S*,22*S*,25*R*)-22-thiospirol-5-en-3-ol acetate) which is the most thermodynamically stable configuration among the isomers. Our findings were in consistent with the previous report.[3]

The undesirable formation of two side products **2b** and **2c** was suggested (Scheme 3). Attack of sulfur in intermediate **E** to **B** occurs at the C-26 to give an intermediate **F**, which affords dimer **2b** by a series of dehydration, redox and hydration. For the formation of trithiane, thioaldehyde **D** is attacked by acetal **C** to form dimeric compound **I**, which further reacts with another thioaldehyde **D** and gives trimer **2c** via the intermediate

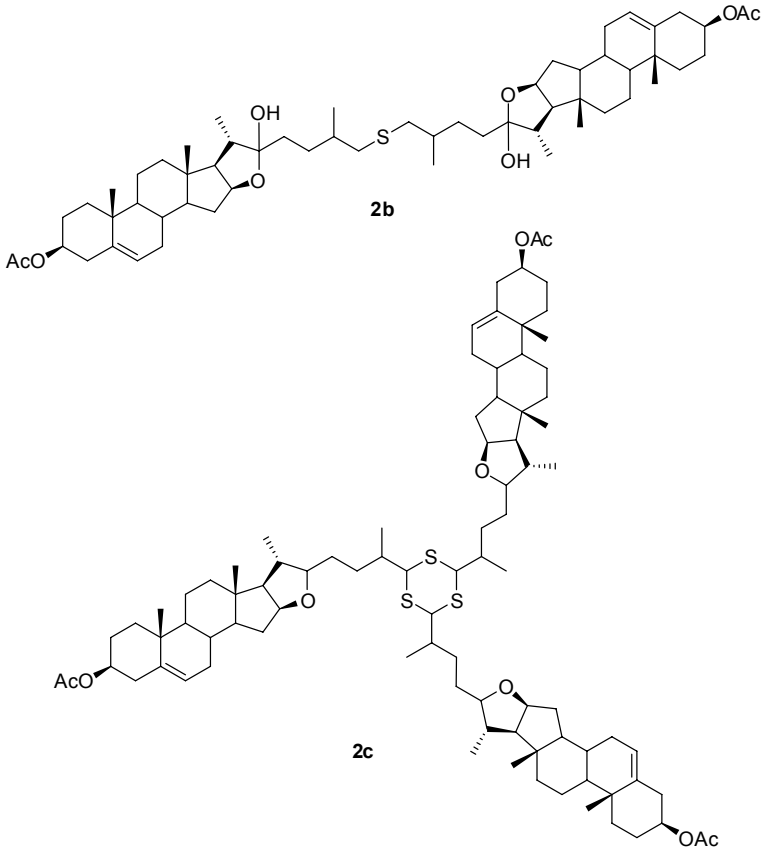
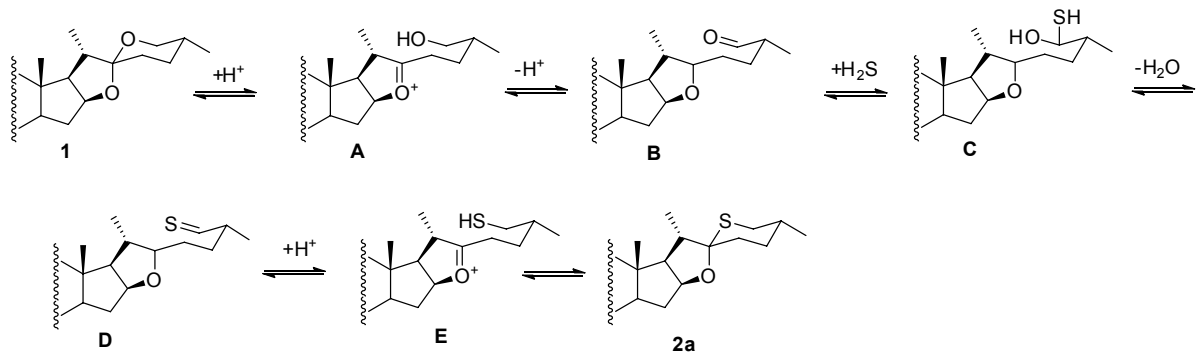
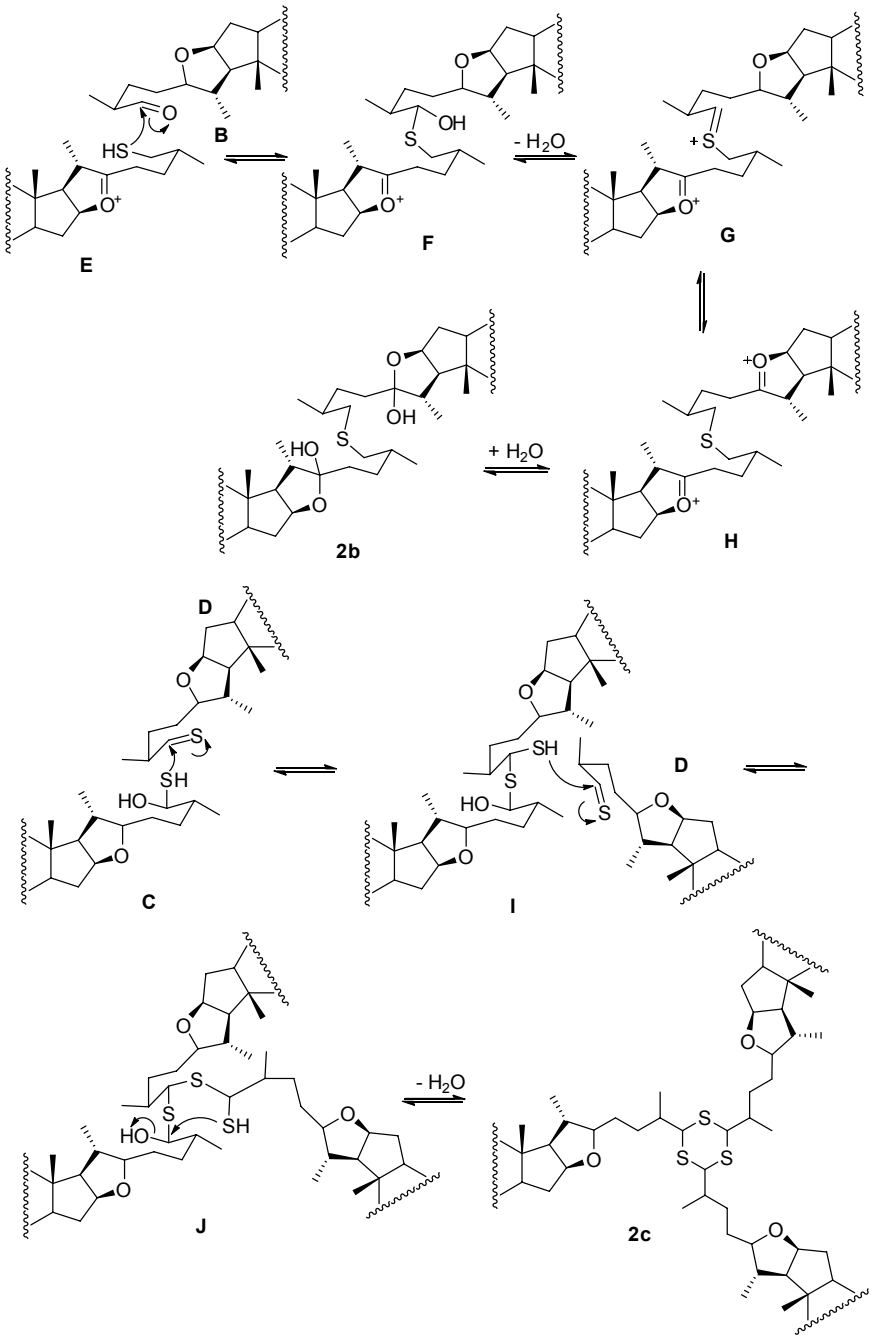


Figure 2 Structure of side products **2b** and **2c**.

Scheme 2 Proposed mechanism for sulfuration of diosgenin acetate

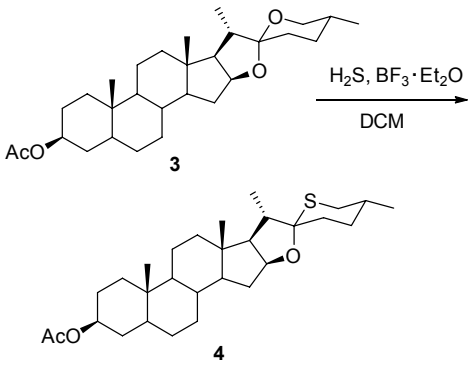


Scheme 3 Proposed mechanism for the formation of **2b** and **2c**



J. These proposed mechanisms showed the possibility of the formation of polymeric residues.

With the optimal reaction conditions in hand, another steroidal sapogenin, tigogenin acetate **3**, was also tested (Eq. 1). The thiotigogenin **4** was afforded in 28% yield.



(1)

Conclusions

In summary, we have developed a BF_3•Et_2O-promoted sulfuration of steroidal sapogenin with hydrogen sulfide, giving the thiodiosgenin and thiotigogenin directly in one step under mild reaction

conditions. Further applications of this synthetic pathway to other steroid-related molecules are currently underway.

Acknowledgement

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