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Reinvestigating the acyl cyclization to the precursor of diptoindonesin G

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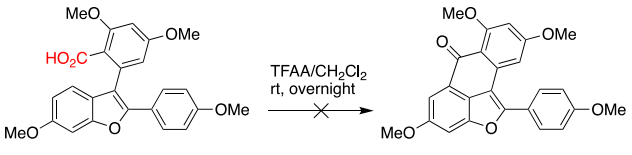
ABSTRACT

We reinvestigated the synthesis of the precursor of diptoindonesin G (**2**) by the intramolecular acyl cyclization of compound **1** or compound **3** in the presence of trifluoroacetic anhydride (TFAA) [**1**,**2**]. Although the reaction of **3** with TFAA generated **2** smoothly as reported, the reaction of **1** with TFAA failed to afford **2**, and compound **1** was partially decomposed under the reaction conditions tested.

Diptoindonesin G can be either naturally isolated from the stem bark of tropical plants such as *Hopea chinensis* [3,4] or totally synthesized [1,2,5,6,7]. It was reported that diptoindonesin G reciprocally stabilizes ERβ and destabilizes ERα in breast cancer cells. Therefore, diptoindonesin G could be used to restore the balance of ERα and ERβ for the treatment of human breast cancer [8]. Recently diptoindonesin G was also found to trigger a switch from basal- to luminal-like breast cancer subtype [9]. To continue our research interest in the field of breast cancer studies, we reinvestigated two synthetic methods for the synthesis of diptoindonesin G reported in literature [1,5].

Kim et al reported several methods for the synthesis of diptoindonesin G [1,2,5]. After we followed Singh and Kim's most recent reported method [1] to prepare intermediate **1** in 7 steps with 40% overall yield (Scheme S1 in SI), we found the reaction of **1** with TFAA (3 M equivalent) in anhydrous dichloromethane under the reported reaction condition (either at room temperature, overnight or at 0 °C – rt for 2 h) did not yield the cyclization product **2** (Scheme 1). The TLC and MS of the reaction mixture indicated compound **1** was partially remaining and partially decomposed (Table S1 and MS in SI). We also tried to increase the reaction time to 72 h and then increase the reaction temperature in refluxing anhydrous dichloromethane (60 °C bath for 6 h) or 1,2-dichloroethane (100 °C bath for 6 h) but still no compound **2** or only trace amount of **2** was detected on TLC. Attempt to isolate new spots by silica gel chromatography was failed, the NMR and MS of the collected samples confirmed mainly the recovery of **1**. The reaction of **1** with TFAA likely first formed anhydride derivative but it might not be stable on TLC so we saw many pots along with the starting material in a line. Side reaction may include the demethylation of the methyl aryl ether of **1** if the reaction was carried out for the long reaction time and high temperature. Other Lewis acids such as $AlCl_3$ and BBr_3 were also examined. We observed compound **1** remained if $AlCl_3$ was used and BBr_3 caused the demethylation of **1** but still no acyl cyclization occurred. The conversion of **1** to **2** remains unsolved.

We then followed another method for the synthesis of diptoindonesin G reported by Kim et al and prepared an intermediate **3** starting from **12** in 8 steps with 36% overall yield [5]. The following reaction of **3** with TFAA in anhydrous dichloromethane produced **2** smoothly (0 °C – rt, 2 h) [2,6]. Compound **2** was purified by silica gel chromatography and could be converted into diptoindonesin G as reported (Scheme 2) [2]. The TLC results for reaction of **3** with TFAA are shown in Table S2.



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Scheme 1. Reaction of **1** with TFAA.

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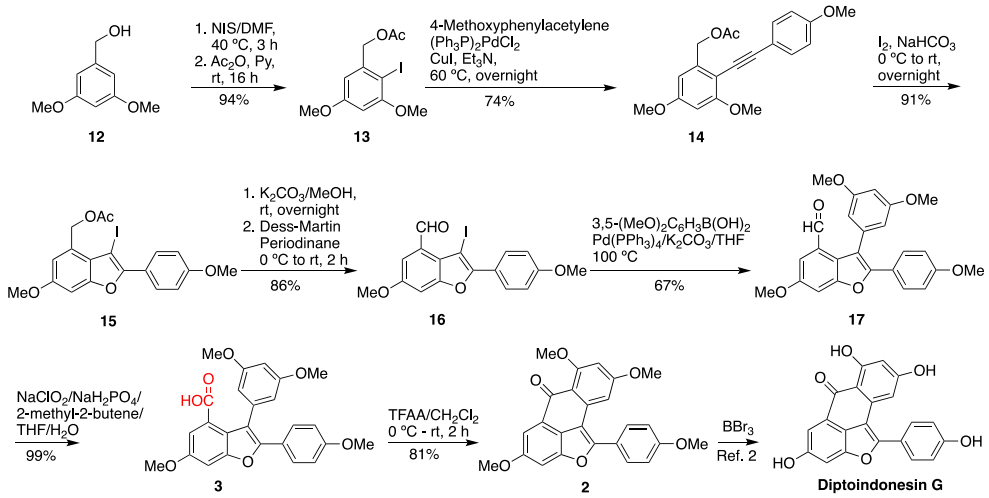
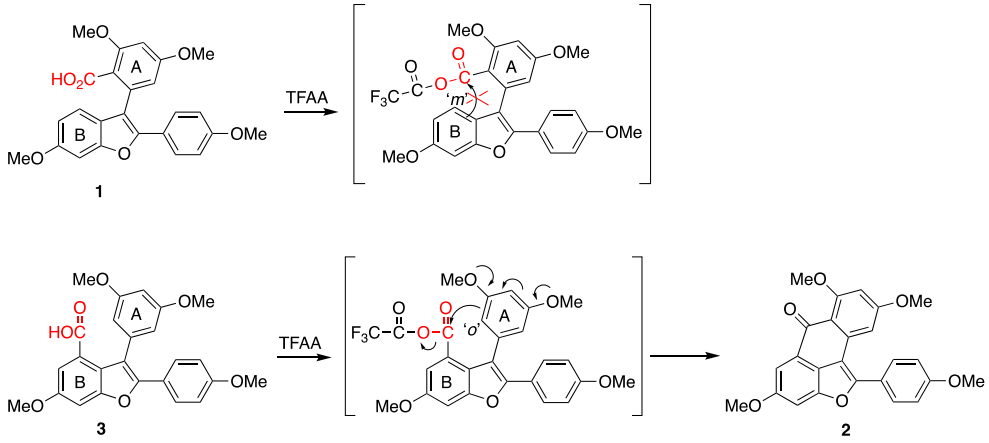


Scheme 2. Preparation of **3** and reaction of **3** with TFAA.



Scheme 3. Proposed reaction mechanisms of **1** or **3** with TFAA.

The differential results could be explained by their differential reactivities of **1** and **3** with TFAA as shown in Scheme 3. As Friedel-Crafts acylation electrophile, the 3-carboxygroup on ring B of **3** is more reactive than the 2-carboxyl group on ring A of **1** due to the deactivation of the strong electron donating property of 3,5-dimethoxyl group of **1**. In the meantime, as a nucleophile the *o*-position of 3,5-dimethoxyphenyl group on ring A of **3** is more reactive than the *m*-position on ring B of **1** due to the activation of the strong electron donating property of 3,5-dimethoxyl group of **3**.

In summary, we conclude the reaction of **1** with TFAA cannot generate the precursor of diptoindonesin G (**2**) under all conditions we tested. Although the reaction of **3** with TFAA generated **2** smoothly as reported, the synthesis of the precursor of diptoindonesin G (**2**) by the acyl cyclization of compound (**1**) is not reproducible and remains unsolved.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152980.

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