Chinese Chemical Letters 26 (2015) 793–796

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Acidic rearrangement of benzyl group in flavone benzyl ethers and its regioselectivity

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ARTICLE INFO

Article history:
Received 21 January 2015
Received in revised form 28 February 2015
Accepted 4 March 2015
Available online 2 April 2015

Keywords:
Benzyl-substituted flavone
Acidic rearrangement of benzyl group
Regioselectivity
Quantum chemical calculation

ABSTRACT

The benzyl-substituted flavone compounds are rare in nature, while some of which have interesting biological activities. The total synthesis of benzyl-substituted flavone derivatives *via* the acidic rearrangement of benzyl groups in flavone benzyl ethers, and the complicated regioselectivity of the rearrangement were reported. The regioselectivity was proposed to be determined by the steric hindrance as well as the ease of electrophilic substitution reaction for benzyl cations at different positions of corresponding debenzylated flavone compounds.

1. Introduction

Flavones are a class of natural products widely distributed in different plants with a wide range of biological activities [1–4]. The different substituents on the basic skeleton contributed to their different biological activities (Fig. 1). The most common substituent on the skeleton is hydroxyl or alkoxy groups. In some flavones, the benzyl group is directly connected to the skeleton, such as compounds **a**–**h** (Fig. 1) [5–8]. These types of compounds are rare in nature, while some of which have interesting biological activities, *e.g.*, compound **h** exhibited multidrug resistance reversal effects on the human tumor cell lines [5]. The introduction of a benzyl group to the flavone backbone of luteolin (compounds **8** and **9** in Fig. 1) was found previously by us to significantly increase its activity to bind with Bcl-2 protein and induce apoptosis of tumor cells [9]. Therefore, the benzyl-substituted flavone compounds are a structural type worthy of further study.

The rearrangement reaction of benzyl groups can be observed in the debenzylation of aryl benzyl ethers, and the related reactions observed in previous reports are mainly involving simple aromatic compounds and aromatic amino compounds [10,11]. Recently, this reaction was successfully used by the Seoane group and us to totally synthesize benzyl-substituted flavone compounds and benzyl-substituted flavanone compounds [9,12]. Compared to the methods used previously [13–16], the method using this rearrangement reaction offers simple protocols and high yields.

In this paper, the total synthesis of benzyl-substituted flavone derivatives *via* the acidic rearrangement of benzyl groups in flavone benzyl ethers was reported. Complicated regioselectivity during the rearrangement of benzyl groups was observed. Then the factors that determine the regioselectivity of benzyl groups during this reaction were discussed.

2. Experimental

Using luteolin as an example, a benzyl group was tried to be introduced to the flavone ring B and ring A. The method of the oxidative cyclization of 2′-hydroxychalcone was selected to build the flavone skeleton [1,17]. The method with trifluoroacetic acid or methylsulfonic acid under heat-refluxing conditions of the rearrangement reaction of the benzyl group was selected [12,18–20]. However, this method required a long reaction time—at least 48 h. Thus, we applied microwaves and found that

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http://dx.doi.org/10.1016/j.cclet.2015.03.035

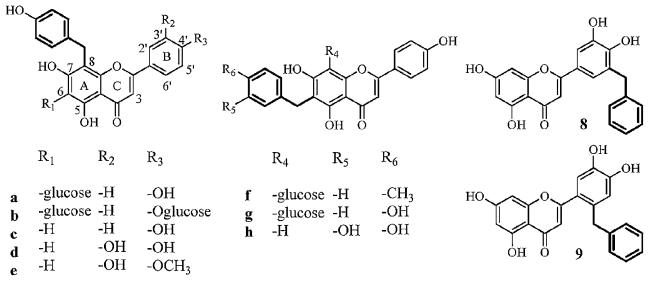


Fig. 1. Basic flavone skeleton and benzyl-substituted flavone compounds.

it significantly shortened the reaction time to less than 30 min. The detailed synthetic route is shown in Scheme 1. Detail materials and methods and the spectra of the products were listed in Supporting information.

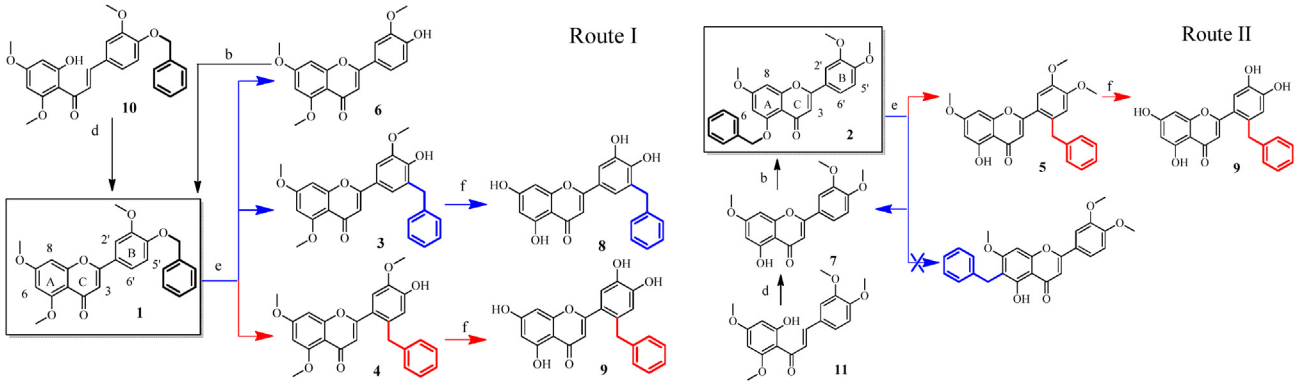
First, to introduce the benzyl group to ring B of luteolin (Scheme 1, Route I), flavone benzyl ethers that benzylate the hydroxyl group on the B ring were needed. Intermediate **10** were synthesized by the known procedure [21,22]. In the presence of iodine/pyridine, the intermediate **10** underwent cyclization to give a flavone benzyl ether compound **1** with 72% yield, in which the hydroxyl groups on the B ring were benzylated. Using microwave, the intermediate **1** underwent a rearrangement reaction in the presence of methylsulfonic acid. This reaction yielded rearrangement products and debenzylated product **6**. Notably, the reaction produced two rearrangement products. Through structural characterization, the benzyl group was found to rearrange to the *ortho* position of the original benzyloxy group (position 5′ of compound **1**) to give a benzylated product **3**. Furthermore, it also rearranged to the *meta* position (position 6′ of compound **1**) to yield the benzylated product **4**. In addition, the proportions of the two products were equivalent, and the yields were 34% and 30%, respectively. Finally, intermediates **3** and **4** underwent demethylation via boron tribromide to obtain the target compounds 3′-benzyl luteolin **8** and 2′-benzyl luteolin **9** with 34% and 30% yields. Although the yield of the single reaction via this route was not high, the intermediate **6** could be re-used to improve the overall yield of the multiple reactions.

Second, a benzyl group was tried to be introduced to the ring A of luteolin (Scheme 1, Route II). Similarly, flavone benzyl ethers, in which the hydroxyl groups on the A ring was benzylated, were obtained. In the preliminary study, the cyclization reaction in the presence of iodine/pyridine was found to generate a byproduct that was demethylated at position 5 of the flavone backbone. In addition, it will gradually become the main product with an increasing amount of iodine and a prolonged reaction time. This side reaction was used to design the following synthetic route. Intermediate **11** were synthesized by the known procedure [21,22]. In the presence of iodine/pyridine, the cyclization of intermediate **11** and demethylation yielded flavone compound **7** with a hydroxy group at position 5 of ring A with 73% yield. In the presence of benzyl chloride, intermediate **7** gave the flavone benzyl ether compound **2**, in which the hydroxyl groups on the A ring is benzylated. Intermediate **2** underwent a rearrangement reaction under microwave conditions in the presence of methylsulfonic acid to yield rearrangement products and debenzylated product **7**, similar to the reaction above. Surprisingly, the benzyl group in the reaction was not rearranged to the position *ortho* of the original benzyloxy group of ring A (position 6 of compound **2**). The structural characterization confirmed that the benzyl group was rearranged to the position 6′ of compound **2** and yielded a benzylated product **5**. The yield of all of the rearrangement products declined (26%) versus compound **1** (64%). Finally, the demethylation of intermediate **5** yielded the same target compound 2′-benzyl luteolin **9** in the presence of boron tribromide. Similarly, the cyclic utilization of intermediate **7** could enhance the overall yield through multiple reactions down this route.

3. Results and discussion

From the total synthesis of benzyl-substituted flavone derivatives, complicated regioselectivity during the rearrangement of the benzyl group in flavone benzyl ether compounds was observed. The benzyl group could be rearranged not only to the position *ortho* of the original benzyloxy group, but also to the *meta* position (the benzyl group of compound **1** rearranged from the 4′ to the 5′ and 6′ positions). Rearrangement to the flavone B ring from the flavone A ring is also possible (the benzyl group of compound **2** rearranged from position 5 to position 6′). This is different from the regioselectivities previously reported for simple aromatic compounds and flavanone compounds, in which the rearrangement of a benzyl group mainly occurred on the *ortho* and *para* positions, and *ortho* rearrangement dominated [10,12]. This may be because previous systems were relatively simple, and the flavone compound system with four substituted groups used here is relatively complicated. This gives a relatively complicated regioselectivity during the rearrangement of the benzyl group.

A reaction mechanism for the acidic rearrangement of the benzyl group in aromatic benzyl ether compounds was proposed by some researchers, based the observation of the intermolecular benzylated product [10,12]. According to this reaction mechanism (Scheme 2), the flavone benzyl ethers were first protonated under



Scheme 1. Synthetic route I and II of benzyl-substituted flavone compounds. Reagents and conditions: a: DMS, K_2CO_3, acetone, r.t.; b: benzyl chloride, K_2CO_3, DMF, reflux; c: 50% KOH, CH_3OH, r.t.; d: I_2, pyridine, reflux; e: MSA, $CHCl_3$, microwave; f: BBr_3, DCM, r.t.