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An efficient synthesis of the phytoestrogen 8-prenylnaringenin from isoxanthohumol with magnesium iodide etherate

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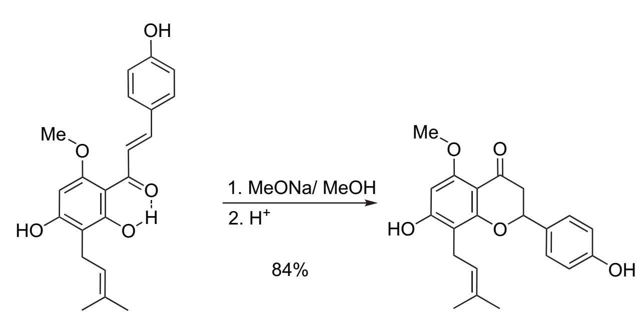
ABSTRACT

Xanthohumol was isolated from supercritical carbon dioxide–spent hop and transformed into isoxanthohumol. The demethylation of isoxanthohumol with the best yield 93% occurred when MgI_2 etherate in anhydrous THF was applied. Salts such as $MgBr_2$, $MgCl_2$, CaI_2, $Mg(OAc)_2$, $Mg(OMe)_2$ were also investigated. A convenient method for the xanthohumol isolation from supercritical carbon dioxide–spent hop is also described.

1. Introduction

The female flowers of hops (*Humulus lupulus* L.) are used in the brewing industry to add flavor and bitterness to beer. The flavor of beer arises mainly from essential oils and the bitterness from iso-alpha-acids. Hops consist of many prenylated chalcones and flavanones.[1] Among them, xanthohumol (**1**) has received much attention in recent years as an anti-cancer[2,3] and antioxidant agent. 8-Prenylnaringenin (**3**) is one of the strongest phytoestrogen known in nature.[4] This compound and its precursors, xanthohumol (**1**) and isoxanthohumol (**2**), may also have anti-breast cancer activity.[5,6] Xanthohumol (**1**) is readily accessible from carbon dioxide-extracted hops[7] where its content ranges up to 1% of dry matter. Isoxanthohumol (**2**) is also present in this source in low concentration, but it can be easily obtained from **1** by dissolving in 1% NaOH and acidification of the reaction mixture (Scheme 1).[8,9] The content of 8-prenylnaringenin (**3**) in hops is 10–100 times lower than the content of **1** and it is hardly accessible from this source. Because of the interesting biological properties and the increase of the commercial importance of **3**, several methods for its synthesis have been proposed. The methods included synthesis from naringenin (up to 45% overall yield),[10–15,16] phloroacetophenone with low yield[17] or xanthohumol (**1**).[9,18] In the last of the above-mentioned studies, **1** was isomerized to **2** using 1% NaOH. The next step was demethylation of **2** to **3** with Lewis acids such as $AlBr_3$, BBr_3 or $MeAlCl_2$ in the presence of collidine (up to 30% yield); $ZnBr_2$, CuI, $ZnBr_2$/CuI $Yb_2(SO_4)_3$/KI or CuI, $Sm(OTf)_3$/KI, $CeCl_3$/LiI (product not detected or low yield); and $Sc(OTf)_3$/KI (92% yield). In an alternative route, the two hydroxyl groups of **2** were protected with using chlorotriisopropylsilane and this product was treated with $AlBr_3$ and the silyl groups deprotected with $(n\text{-Bu})_4NF$ (73% overall yield of **3**).



1 **2**

Scheme 1. Cyclization of xanthohumol (**1**) to isoxanthohumol (**2**).

In this paper we report a convenient method of demethylation of isoxanthohumol (**2**) using magnesium iodide. Magnesium iodide etherate is the reagent for the demethylation of a methoxy group especially at the *ortho*-position to the carbonyl group.[19] Such an arrangement is present in **2**. This complex was previously applied

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in the regioselective demethylation of 5-acetyl-4,6-dimethoxy-2-isopropenyl-2,3-dihydrobenzofuran[20] and substituted 2,6-dimethoxybenzaldehydes.[21]

2. Results and discussion

The crucial step in the synthesis of 8-prenylnaringenin (**3**) from xanthohumol (**1**) is the demethylation of isoxanthohumol intermediate product (**2**). For the first time, we have used magnesium and calcium salts for the demethylation of **2**. Magnesium iodide proved to be a powerful, convenient, and inexpensive reagent, in contrast to the scandium salts.

The starting compound, xanthohumol (**1**), was isolated from supercritical carbon dioxide–spent hop by the extraction with acetone, purification on silica gel, and subsequent crystallization. Treatment with 1% NaOH as described in the literature,[9] acidification and purification on silica gel gave isoxanthohumol (**2**) with 84% yield (Scheme 1). Scheme 2 shows the route of the demethylation of **2**, based on a previously proposed mechanism.[21] Isoxanthohumol (**2**) forms a complex with MgX_2. The next step is the subsequent thermal elimination of volatile MeX to form the magnesium salt of 8-prenylnaringenin, which is converted in acidic conditions into **3**.

The results of the demethylation of substrates **1** and **2** are presented in Table 1. As a reaction medium we have chosen THF, which improved the solubility of the reagents. In the case of Et_2O the reaction occurred very slowly because the reagents, isoxanthohumol (**2**) and 8-prenylnaringenin, had low solubility.

We have found that the best yields, 88% and 93%, were obtained using magnesium iodide etherate under strictly anhydrous conditions. In the case of $MgBr_2$ and $MgCl_2$, the reaction was worse and 39% and 4% yields were obtained, respectively. Although we did not find in literature the detailed mechanism of this reaction, it seems that nucleophilic attack of an anion of halogen on the methyl group is involved in the demethylation reaction. Such a mechanism has been proposed for the catalytic dealkylation of aryl ethers at the position *ortho* to the carbonyl group by LiCl.[22] Taking this into consideration, MgI_2 works the best because the iodide anion is a more powerful nucleophile than bromide or chloride anions. As shown in Table 1, CaI_2 was less effective than MgI_2 in promoting the demethylation reaction and was able to produce 8-prenylnaringenin with 11% yield after 72 h of reaction. In this case, 73% of substrate was recovered. $Mg(OAc)_2$ and $Mg(OMe)_2$ were not useful and we did not detect 8-prenynaringenin after the reaction.

Table 1
Demethylation of xanthohumol (**1**) and isoxanthohumol (**2**)

Entry	Substrate	Metal salt	*t* (h)	Yield[a] (%)	Recycled **1** or **2**[b] (%)
1	**2**	MgI_2	12	88.1 (93.0)[c]	0 (0)[c]
2	**2**	$MgBr_2$	12	38.6	0
3	**2**	$MgCl_2$	12	3.9[d]	81.7
4	**2**	CaI_2	72	11.0	73.2
5	**2**	$Mg(OAc)_2$	48	0, Many prod.[e]	60.3
6	**2**	$Mg(OMe)_2$	48	0	76.0
7	**1**	MgI_2	48	Many prod.[e]	0

[a] Isolated yield, the reaction was carried out with 50 mg of **1** or **2**.
[b] Yield based on HPLC analysis.
[c] The reaction was carried out with 400 mg of **2**.
[d] 6.2 mg of the mixture of mainly two compounds with the same R_f on TLC was isolated, yield based on HPLC analysis of this mixture.
[e] Complicated product mixture.

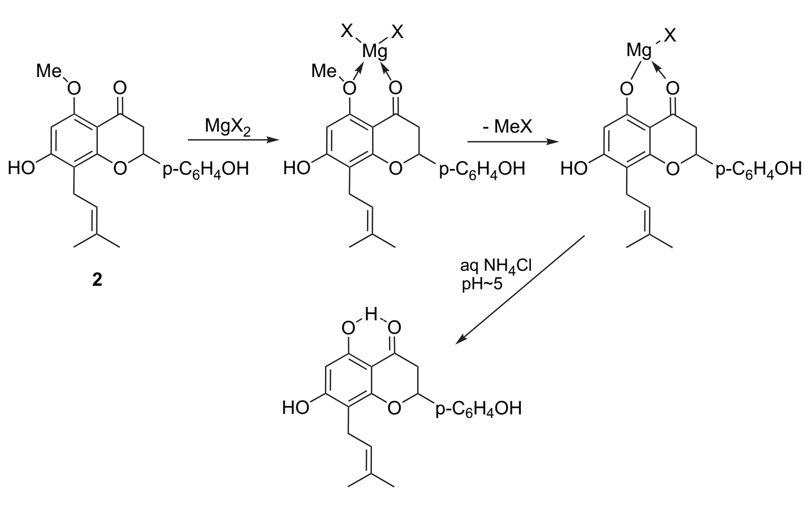
$Mg(OAc)_2$ was used as a donor of weak nucleophilic group AcO^-. $Mg(OMe)_2$ was applied as a donor of strong nucleophile MeO^- (also a strong base, which reacts with the hydroxyl groups of isoxanthohumol). If the reaction could occur, dimethyl ether should be formed, which as a gas could be eliminated from the reaction medium. It would promote the reaction. Our attempt at applying the procedure to xanthohumol demethylation was unsuccessful and we observed on HPLC and TLC many compounds in the reaction mixture. It can be connected with the fact that the carbonyl group and hydroxyl group form a strong intramolecular hydrogen bond in xanthohumol (**1**), Scheme 1, and it is not able to create a complex with magnesium iodide similar to that shown in Scheme 2.

In conclusion, we have developed an efficient and simple method for the synthesis of 8-prenylnaringenin. Further work toward the demethylation of isoxanthohumol derivatives using magnesium iodide is underway in our laboratory. Work in progress will be reported in due course.

3. Experimental

3.1. General experimental information

Spent hop originating from supercritical carbon dioxide extraction of hop variety Marynka, extracted at the beginning of December 2005, was obtained from Production Plant of Hop Extracts of Fertilizer Institute, Puławy, Poland. Moisture content of spent hop was 5.34%. All the remaining reagents were purchased from Fluka. Analytical thin-layer chromatography was carried out



Scheme 2. Demethylation of isoxanthohumol with magnesium halogenates.