

## Pechmann Reaction Promoted by Boron Trifluoride Dihydrate

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**Abstract:** The Pechmann reaction of substituted phenols **1a-e** with methyl acetoacetate (**2**) can be activated by boron trifluoride dihydrate (**3**) to give the corresponding 4-methylcoumarin derivatives **4a-e** in excellent yield (98-99 %).

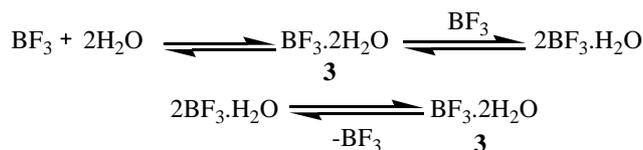
**Keywords:** Pechmann Reaction, 4-methylcoumarins, boron trifluoride dihydrate.

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### Introduction

The coumarin moiety is widespread in nature and its derivatives find applications as fragrances, pharmaceuticals and agrochemicals [1]. Some 4-methylcoumarins are also useful as antioxidants in lipid peroxidation [2]. Their 7-methoxy- and 7-ethoxy derivatives have remained the most selective inhibitors for the coumarin 7-hydroxylase (Coh) enzyme [3,4]. The main method for the synthesis of coumarins is the Pechmann reaction of substituted phenols of type **1** with methyl, **2**, or ethyl acetoacetate in the presence of protonic acid (conc. H<sub>2</sub>SO<sub>4</sub>), Lewis acids (AlCl<sub>3</sub>, ZnCl<sub>2</sub>, ZnCl<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>, ZrCl<sub>4</sub> etc.), dehydrating agents (P<sub>2</sub>O<sub>5</sub>) or montmorillonite clay [5-10]. The mechanism of this condensation involves three reactions: hydroxyalkylation, transesterification, and dehydration, which occur concomitantly condensing the two reactants to form the coumarin heterocycle [5]. Recently, solid acid catalysis has been found effective in the synthesis of 7-hydroxy-4-methylcoumarin (**4a**), giving moderate yields (40-50 %) using commercially available solid acid catalysts (Amberlyst IR 120 or Nafion 417) [11]. In 1934 Meerwein and Pannwitz reported that by reaction of boron trifluoride with water two kinds of products are formed – boron trifluoride dihydrate (**3**) and boron trifluoride monohydrate (Scheme 1) [12].

## Scheme 1

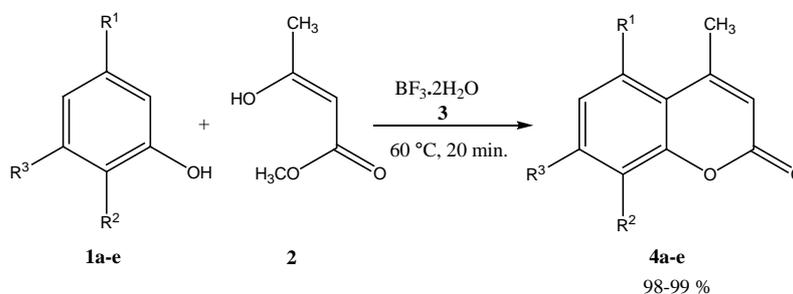


The monohydrate is a fuming liquid, too unstable to be stored at room temperature. It loses one mole of  $\text{BF}_3$  to form the dihydrate **3** (Scheme 1) [12]. The boron trifluoride monohydrate is a known superacid and several applications in organic syntheses have already been published [13-17]. In contrast to this, the dihydrate **3** is more stable and can be even distilled under reduced pressure. Meerwein and Pannwitz also described that the reaction of **3** with water is reversible and the starting compound could be recovered [12]. Although its crystal structure was determined [18] nothing was to be found in the literature about its chemistry, e.g. its application in organic synthesis, and to the best of our knowledge, the use of **3** as an activator for organic reactions has not been reported until now. The aim of the present work was to study the use of boron trifluoride dihydrate (**3**) as a promoting reagent for the *Pechmann* condensation.

## Results and Discussion

The reaction of substituted phenols **1a-e** with methyl acetoacetate (**2**) was carried out at room temperature and at 60 °C (Scheme 2).

## Scheme 2



1.4	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
a	H	H	OH
b	H	OH	OH
c	OH	H	OH
d	H	H	OMe
e	H	H	OEt

In contrast to the *Pechmann* synthesis activated by conc.  $\text{H}_2\text{SO}_4$ , the reaction promoted by boron trifluoride dihydrate (**3**) is not perceivably exothermic and no cooling is necessary. This could be an important advantage for industrial applications. Resorcinol (**1a**) gave 7-hydroxy-4-methylcoumarin (**4a**) in yields ranging from 90-95 % under stirring for 3 hours at 18-20 °C and almost quantitatively (99 %) after 20 minutes at 60 °C. Of all obtained coumarins only the product **4a** is soluble in **3** at room temperature.

If polyhydroxy benzenes such as pyrogallol (**1b**) or phloroglucinol (**1c**) are used, the condensation with **2** slows down at 18-20 °C, probably due to the lower solubility of the starting compounds in **3**. The reaction was complete in 10-12 hours. By heating at 60 °C a clear solution was formed from which within 5 minutes the 7,8-dihydroxy-4-methylcoumarin (**4b**) and the 5,7-dihydroxy-4-methylcoumarin (**4c**) precipitated. The yields at both reaction conditions were excellent (98-99 %, Table 1).

**Table 1.** Substituted 4-methylcoumarins **4a-e** produced *via* Scheme 2

Product <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	m.p. <sup>b</sup> / Lit. m.p. (°C)	Yield, %	Reaction time at 60 °C, min
<b>4a</b>	H	H	OH	184-186 / 186 [19]	99	20
<b>4b</b>	H	OH	OH	235-237 / 233-235 [19]	99	5
<b>4c</b>	OH	H	OH	289-291 / 286 <sup>c</sup> [20]	98	5
<b>4d</b>	H	H	OMe	158-160 / 160 [21]	98	20
<b>4e</b>	H	H	OEt	113-115 / 115 [22]	99	20

<sup>a</sup>The identity of all the products was confirmed by comparison of the m.p.'s, R<sub>f</sub> values and IR spectra with authentic samples; <sup>b</sup> Recrystallization solvents: for **4a** 50 % EtOH, for **4b** H<sub>2</sub>O, for **4c-e** EtOH; <sup>c</sup> From MeOH/H<sub>2</sub>O.

The condensation of methyl acetoacetate (**2**) with 3-methoxy- (**1d**) and 3-ethoxyphenol (**1e**) was also successful. At room temperature the corresponding 7-methoxy- (**4d**) and 7-ethoxy-4-methylcoumarin (**4e**) were isolated after 15-18 hours in very good yields (85-90 %). If the reactions were carried out at 60 °C for 20 minutes, the yields increased to 98-99 % (Table 1). In order to compare the activation ability of **3** with that of conc. H<sub>2</sub>SO<sub>4</sub> for the synthesis of **4d** and **4e**, we repeated the same experiments using concentrated sulfuric acid, but the yields were always lower (40-70 %).

To isolate the products **4a-e**, the reaction mixtures were poured into 50 g of crushed ice and the solids formed were collected by filtration. The boron trifluoride dihydrate (**3**) can be reused several times after mild evaporation of the aqueous phase under reduced pressure.

## Conclusions

In summary, to the best of our knowledge the use of the boron trifluoride dihydrate (**3**) as an activator in organic synthesis is now reported by us for the first time. The title compound **3** can be used in the *Pechmann* condensation, giving substituted 4-methylcoumarins in excellent yields (98-99 %). The possibility of reusing **3** also provides a cheaper and easier method for the synthesis of **4**.

## Experimental

### General procedure

A mixture of the corresponding phenol **1a-e** (30 mmol), methyl acetoacetate (**2**, 3.48 g, 30 mmol) and boron trifluoride dihydrate (**3**, 20.8 g, 200 mmol) was heated at 60 °C for 20 minutes. After cooling to room temperature, the mixture was poured into 50 g of crushed ice. The crystals formed were filtered off, washed with water and air dried to give crude, tlc-pure products **4a-e** (POLYGRAM SIL G/UV<sub>254</sub> plates, solvent CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>COOC<sub>2</sub>H<sub>5</sub> 9:1). If necessary the products can be recrystallized from the solvents given in Table 1.

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*Sample Availability:* Available from the authors.