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.

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. H₂SO₄), Lewis acids (AlCl₃, ZnCl₂, ZnCl₂/Al₂O₃, ZrCl₄ etc.), dehydrating agents (P₂O₅) 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].
The monohydrate is a fuming liquid, too unstable to be stored at room temperature. It loses one mole of 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).

In contrast to the Pechmann synthesis activated by conc. H$_2$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 | 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 |
|---------|------------|------------|------------|-------------------------------|-----------|--------------------------|
| 4a      | H          | H          | OH         | 184-186 / 186 [19]             | 99        | 20                       |
| 4b      | H          | OH         | OH         | 235-237 / 233-235 [19]         | 99        | 5                        |
| 4c      | OH         | H          | OH         | 289-291 / 286<sup>c</sup> [20] | 98        | 5                        |
| 4d      | H          | H          | OMe        | 158-160 / 160 [21]             | 98        | 20                       |
| 4e      | 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/UV254 plates, solvent CH₂Cl₂:CH₃COOC₂H₅ 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.

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