



## Easy eco-friendly phenonium ion production from phenethyl alcohols in dimethyl carbonate



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### ABSTRACT

An efficient and simple one-pot procedure for selective etherification of 2-aryl-ethylalcohols has been achieved through Amberlyst 15-catalyzed reaction in dimethyl carbonate (DMC). Moreover, the polymer catalyst could be recovered and reused with no effect on its activity. The reaction mechanism involves the formation of phenonium ion which has been demonstrated by a C–C bond forming reaction. Theoretical studies are in agreement with and thus explain experimental results.

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The phenonium ion was first described by Cram<sup>1–3</sup> in the 40s as an intermediate in the solvolysis reactions of phenethyl chlorides and tosylates. In the 70s Olah and Porter<sup>4,5</sup> characterized via NMR spectroscopy some stable phenonium ions prepared from their chloride precursors in  $\text{SbF}_5/\text{SO}_2\text{ClF}$  solution. The lifetime of these cations strictly depends on the ring substitution.<sup>6</sup> After the pioneering work of Cram and Olah, little attention has been paid to the exploitation of new synthetic routes to generate the phenonium ion.<sup>7,8</sup>

In the last three decades the interest in dimethyl carbonate (DMC) as an eco-sustainable reagent has grown.<sup>9,10</sup> Recently it has been largely used as an environmentally friendly and safe medium for its low toxicity and biodegradability. As reagent, DMC has been widely employed as an electrophile in the methylation reaction.<sup>11</sup>

In recent years, the use of solid acidic catalyst has attracted considerable attention.<sup>12</sup> In this regard, Amberlyst 15 possesses unique properties such as environmental compatibility, nontoxic, reusability, chemical, physical stabilities, and durability. Owing to the numerous advantages associated with this cheap and non-hazardous polymer, Amberlyst 15 has been explored as a powerful catalyst in various organic reactions.<sup>13</sup>

In the course of our research on the selective protection of primary alcohol in tyrosol (**1**), we became interested in exploring the

reactivity of  $\beta$ -phenethyl carbonates. We have already reported that selective protection can be achieved by using DMC with basic or acid catalysis,<sup>14,15</sup> obtaining the corresponding carboxymethyl esters in excellent yield (Fig. 1).

Herein we describe a one-pot synthesis of 4-hydroxyphenethyl methyl ether (**1b**) and its related compounds (Scheme 1).

Initial attempts to prepare 4-hydroxyphenethyl methyl ether (**1b**) were performed by reacting **1** in the presence of  $\text{H}_2\text{SO}_4$ . However, a large excess of  $\text{H}_2\text{SO}_4$  was necessary for a full conversion of the substrate due to the contemporary formation of dimethyl sulfate as the by-product.<sup>16</sup> In order to avoid this side reaction,  $\text{H}_2\text{SO}_4$  was replaced by Amberlyst 15. Catalysis via Amberlyst 15 is considered inexpensive and eco-sustainable conditions due to the possibility of recycling the heterogeneous catalyst. In our case up to five cycles can be performed without apparent loss of efficiency. In the procedure using Amberlyst 15 as the catalyst a cascade reaction can be promoted when **1** is refluxed in DMC in the presence of Amberlyst 15 leading directly to **1b** with no need to isolate the carboxymethyl ester (**1a**) (Scheme 1). The reported procedure is,

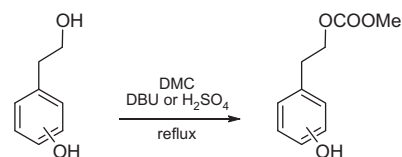
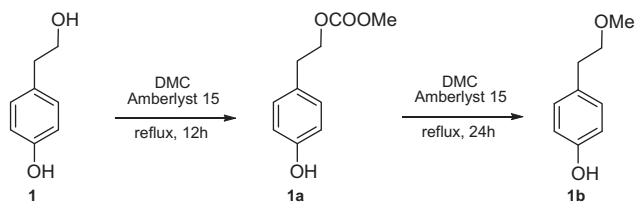


Figure 1. Selective carboxymethylation of primary alcohols.

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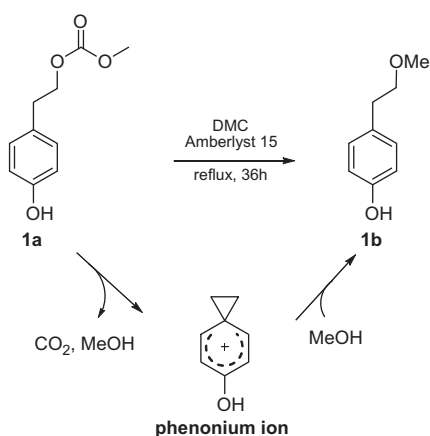
**Scheme 1.** One-pot synthesis of 4-hydroxyphenethyl methyl ether (**1b**).

to our knowledge, the first example of selective etherification of primary alcohols in the presence of phenols.<sup>17</sup>

The proposed reaction mechanism involves the formation of phenonium ion by the loss of CO<sub>2</sub> and methanol, the latter acting as a nucleophile for the completion of the process (Scheme 2).

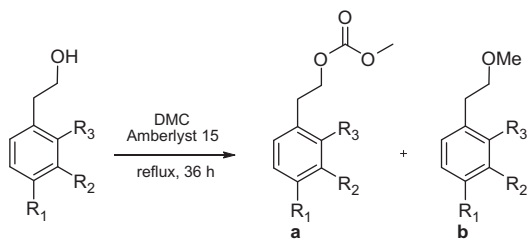
Further investigations were carried out to support the formation of phenonium ion as the intermediate in the process (Table 1).

The results obtained suggest that the phenonium ion is stabilized by electron donating groups in *ortho* and *para* positions (Table 1 entries 2, 4, 5, and 6) and destabilized by electron withdrawing groups (Table 1 entries 7 and 8). Further evidences



**Scheme 2.** Proposed mechanism.

**Table 1**  
Scope of selective methylation reaction

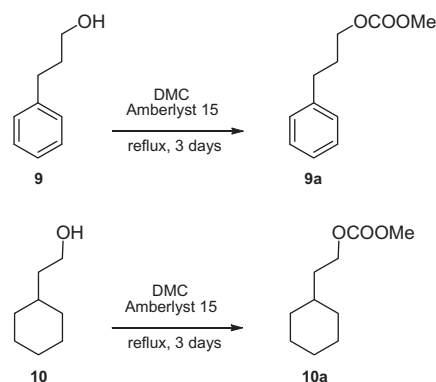


Entry	Substrate	Yield product <b>a</b> <sup>a</sup> (%)	Yield product <b>b</b> <sup>a</sup> (%)
1	R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = H	79	14
2	R <sub>1</sub> = OMe, R <sub>2</sub> = R <sub>3</sub> = H	—	>95
3	R <sub>2</sub> = OMe, R <sub>1</sub> = R <sub>3</sub> = H	72	21
4	R <sub>3</sub> = OMe, R <sub>1</sub> = R <sub>2</sub> = H	—	>95
5	R <sub>1</sub> = OH, R <sub>2</sub> = R <sub>3</sub> = H	—	>95
6	R <sub>1</sub> = R <sub>2</sub> = OH, R <sub>3</sub> = H	—	>95
7	R <sub>1</sub> = NO <sub>2</sub> , R <sub>2</sub> = R <sub>3</sub> = H	81	9
8	R <sub>2</sub> = CF <sub>3</sub> , R <sub>1</sub> = R <sub>3</sub> = H	78	11

<sup>a</sup> All yields refer to isolated products.

to indirectly support the suggested mechanism could be obtained by subjecting 3-phenylpropan-1-ol (**9**) and 2-cyclohexylethanol (**10**) to the reaction conditions (Scheme 3).

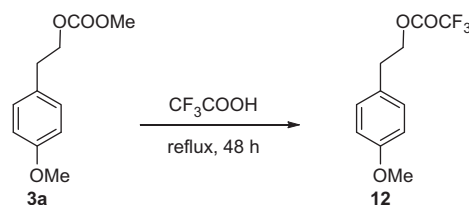
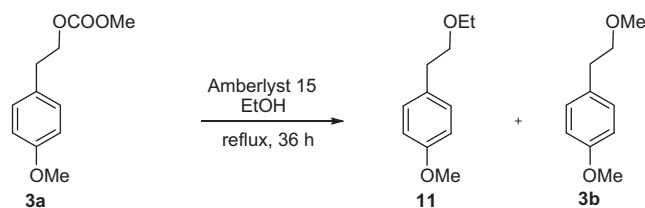
As expected, substrates **9** and **10** gave exclusively the carboxy-methyl ester derivatives (**9a** and **10a** respectively), even when prolonged reaction times are used (Scheme 3).



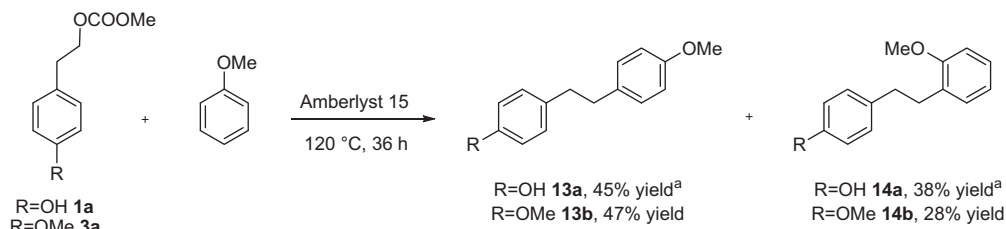
**Scheme 3.** Indirect proof of the proposed mechanism.

**Table 2**  
Free energy differences (in Kcal/mol) obtained at B3LYP/6-311+g(d,p)/PCM level of theory

R	a	Phenonium ion	b
H	0	+0.40	-15.06
<i>o</i> -OMe	0	-6.29	-15.01
<i>m</i> -OMe	0	+2.19	-15.06
<i>p</i> -OMe	0	-7.35	-15.22
NO <sub>2</sub>	0	+12.00	-15.54



**Scheme 4.** Reaction of **3b** in the presence of different nucleophiles.



**Scheme 5.** C–C bond formation. (a) Products **13a** and **14a** were characterized as acetyl derivatives. Yields refer to the corresponding acetylated derivatives.

Theoretical calculations are in agreement with experimental data. (Table 2) We have considered three systems to understand the differences in reactivity, the carboxymethylester (system a-H), the *o*-, *m*-, *p*-MetO-carboxymethyl ester (systems a-*o*-OMet, a-*m*-OMet and a-*p*-OMet), and the *m*-NO<sub>2</sub>-carboxymethyl ester (system a-NO<sub>2</sub>). They were chosen since they are representative of the electron donating and electron withdrawing groups for which different reactivities were observed. For all the systems we have optimized the structure with the B3LYP/6-311G(d,p)/PCM method.<sup>18</sup> From the resulting minima we have investigated the energetics of the reaction corresponding to the formation of the intermediate phenonium ion where the proton is donated by H<sub>2</sub>SO<sub>4</sub>, thus releasing CO<sub>2</sub> and MeOH, and then the final product. Results are reported in Table 2 where for each reaction the reference relative energy was set for system a. As clearly shown from DFT results, the phenonium ion is stabilized in the case of an electron donating group in positions *ortho* and *para*, while it is not favoured in the case of the same electron donating group in position *meta* and an electron withdrawing group. On the other hand the final product has roughly the same energy whatever is the substituent group on the ring. This confirms the reaction pathway suggested by experiments, and the formation of the phenonium ion is the determining step allowing (or not) the reaction to proceed further.

The ease of producing a phenonium ion paves the way for new synthetic methodologies. As an example, performing the reaction in ethanol led to the corresponding ethyl ether (**11**) in good yield while in TFA the corresponding trifluoroacetate (**12**) was the only product (Scheme 4).

Even though in the literature it is described that the phenonium ion is usually formed by solvolysis,<sup>19</sup> in our case the ion is produced by the decomposition of carboxymethyl ester, allowing to be potentially exploited by reacting with different nucleophiles. A first example of the practicality of this methodology is the carbon–carbon bond formation using anisole as the solvent/reactant by which stilbene precursors can be obtained. (Scheme 5)

In summary, a new eco-friendly and efficient method to produce phenonium ion is reported and some potential applications in synthesis are described. Remarkably, this approach allows the possibility to induce a carbon–carbon bond formation giving access to the important class of stilbenes. The process was optimized in order to reduce environmental impact. This approach is highly efficient and hence constitutes a new high-yielding and versatile methodology for the synthesis of functionalized phenethylic intermediates.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.06.122>.

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