Convenient O-Methylation of Phenols with Dimethyl Carbonate

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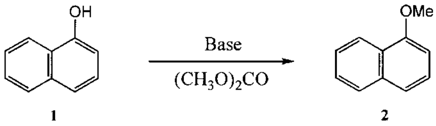
Received 7 July 1998

Abstract: Reaction of phenols in dimethyl carbonate in the presence of cesium carbonate at 120-160° C gave aryl methyl ethers in good yields, whereas the reaction of aliphatic alcohols gave the corresponding alkyl carbonates. This method provides a useful synthetic method for preparation of various aryl methyl ethers without using toxic methyl iodide or dimethyl sulfate. O-Methylation of the aromatic hydroxy group of estradiol was carried out in 2 steps without protection of the alcoholic hydroxy group in the same molecule.

Replacement of chemical processes using toxic materials by those with safes materials is an urgent issue in organic synthesis. The O-methylation reaction of phenols is important in organic synthesis, however, toxic dimethyl sulfate or methyl iodide is used generally as a methylation agent. Dimethyl carbonate is produced cheaply on an industrial scale by the catalytic oxidative carbonylation of methanol as a non-phosgene process [1-3]. Although dimethyl carbonate is recognized as a useful methoxycarbonylating reagent, its synthetic use as a methylating agent is rare [4, 5]. In this paper we describe that methylation of phenols can be carried out using dimethyl carbonate in good yields in the presence of a catalytic amount of base.

As shown in Table **1** the reactions using sodium carbonate or potassium carbonate were very slow. The use of Cs_2CO_3 gave the best result and the reaction of 1-naphthol (**1**) in the presence of Cs_2CO_3 (0.25 eq.) in dimethyl carbonate at 120° C for 4 h gave O-methyl-1-naphthol (**2**) in 100% yield [6].



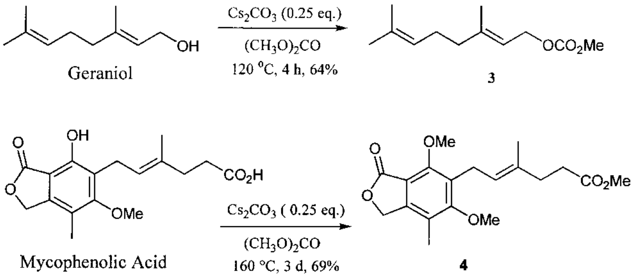
1 **2**

Table 1. Methylation of 1-naphthol (**1**)

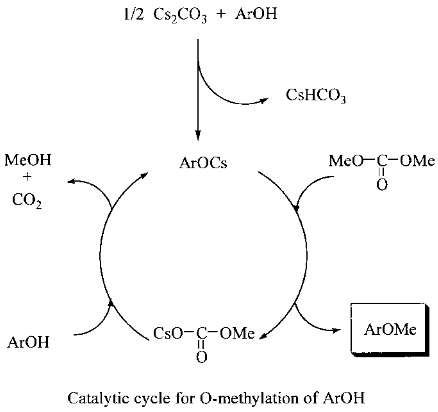
BASE	TEMP (°C)	TIME	YIELD (%)
$Na_2CO_3$$^{(a)}$	120	7 days	91
	150	3 days	72
$K_2CO_3$$^{(a)}$	120	22 hrs	69
	140	16 hrs	68
$K_2CO_3$$^{(b)}$	140	16 hrs	87
$Cs_2CO_3$$^{(a)}$	120	4 hrs	100

(a) Na_2CO_3 = 0.25 eq., K_2CO_3 = 0.25 eq., Cs_2CO_3 = 0.25 eq.
(b) K_2CO_3 = 1 eq.

Various aromatic hydroxy compounds were converted to the corresponding O-methyl ethers but the reaction of geraniol gave methyl geranyl carbonate as the sole product (Scheme **1**). These results indicate that the phenol anion attacks the methyl group of dimethyl carbonate directly, whereas the alcoholic anion attacks the carbonyl groups. Furthermore, the reaction proceeded with a catalytic amount of Cs_2CO_3; cesium methyl carbonate, which is generated after formation of a methyl phenyl ether by the reaction of the phenol anion with dimethyl carbonate, works as a base again as shown in Scheme **2** [7, 8]. Carboxylic acids can be also methylated to their methyl esters, thus, both the phenolic hydroxide and the carboxylic acid of mycophenolic acid were methylated at 160 °C to give **4** in 69% yield (Scheme **1**).



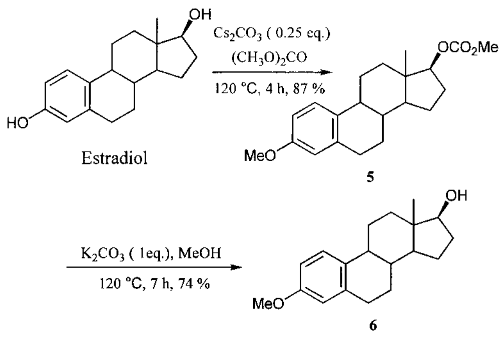
Scheme 1



Catalytic cycle for O-methylation of ArOH

Scheme 2

Selective methylation of estradiol is possible by applying this method. Thus, methylation of estradiol in dimethyl carbonate at 120 °C for 4 h gave 3O-methyl-17O-methoxycarbonylestradiol (**5**) in 87% yield. Treatment of the carbonate (**5**) with K_2CO_3 in methanol gave 3O-methylestradiol (**6**) in 74% yield (Scheme **3**).



Selective methylation of estradiol

Scheme 3

In addition to the advantage that this reaction is clean, isolation of the products is carried out with ease by concentration before purification. Therefore this method provides a useful synthetic method for methylation of phenols, especially in a large scale.

Acknowledgment: This research was supported by the Materials Characterization Central Laboratory, Waseda University, for NMR and HRMS measurement. This research was carried out as a part of the research program in a Grant-in-Aid for Scientific Research on Priority Areas (No 10132261) of Education, Science, Sports, and Culture of Japan and the Materials Research Laboratory for Bioscience and Photonics, Waseda University. YL thanks Iwaki Foundation for Foreign Students for financial support.

References and notes

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(6) Typical experiment for Table **1**. Methylation of 1- naphthol (**1**) (36.2 mg), cesium carbonate (20.4 mg), and dimethyl carbonate (2 ml) were placed in a test tube equipped with a sealed cap. The test tube was heated at 120°C for 4 h. After the mixture was cooled to room temperature, the volatile materials were evaporated in vacuo. The residue was chromatographed on SiO_2 with 5% EtOAc - Hexane to give O-methyl-1-naphthol (**2**) (40 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.9 (3H, s), 6.72 (1H, dd, J = 1.1 Hz, J = 2.2 Hz), 7.27 -7.35 (4H, m), 7.65 - 7.75 (1H, m), 8.13 - 8.22 (1H, m)
IR (ν, cm^{-1}) : 3053 - 3000, 2950 - 2810, 1650, 1580, 1510, 1465, 1450, 1440, 1390, 1265, 1240.

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