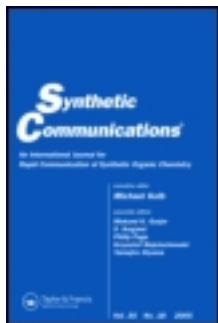


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### O-Benzoylation of Phloroglucinol via Phloroglucinol Triacetate

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## ***O*-BENZYLATION OF PHLOROGLUCINOL VIA PHLOROGLUCINOL TRIACETATE**

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**Abstract:** *O*-Benzylation of phloroglucinol, which was difficult due to *C*-benzylation, was successfully carried out by a method using phloroglucinol triacetate as an intermediate.

Benzyl ether is a popular protecting group of phenolic hydroxyl groups in organic synthesis, because this ether is stable under basic or mildly acidic conditions but is readily cleaved by hydrogenolysis.<sup>1</sup> Benzylation is generally conducted by using benzyl halide with anhydrous potassium carbonate in aprotic polar solvent such as acetone, *N,N*-dimethylformamide (DMF) and so on.<sup>1</sup> However, benzylation of phenols with high electron-density such as phloroglucinol (**1**), gives a mixture of *O*- and *C*-benzylated products, which lead to a low yield of the *O*-benzylated products, and it is also difficult to separate them even by the chromatographic techniques.<sup>2</sup>

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Benzyl *p*-toluenesulphonate<sup>3</sup> as a benzylation reagent and hexamethylphosphoramide<sup>4</sup> as a benzylation solvent have been reported for selective *O*-benzylation, but the former reagent is not commercial available and is difficult to be prepared because of its instability, and the latter solvent is very expensive.

In this communication, highly regiospecific *O*-benzylation method of phloroglucinol using phloroglucinol triacetate (**2**) as a starting material whose electron-density is reduced by the acetyl groups.

*C*-Benzylated product is formed by the attack of benzyl halide on carbon atoms of the aromatic ring. Such reaction may be prevented due to reducing electron-density by introducing electron withdrawing acetyl groups. This method is based on the simultaneous benzylation with the partial hydrolysis of phloroglucinol triacetate under suitable reaction conditions.

By adding water dropwise into the mixture of compound **2**, benzyl chloride, and sodium hydride in DMF, compound **2** was converted into phloroglucinol tribenzyl ether (**3**) quantitatively (FIG. 1). None of the *C*-benzylated products were detected under these reaction conditions, although general benzylation method using benzyl chloride and potassium carbonate in DMF gave a mixture of *O*-benzylated (**3**) and *C*-benzylated products (**4**) with 1 : 1 molar ratio. The structure of these products were identified by the comparison of their <sup>1</sup>H-NMR spectra with those reported by Deme.<sup>2</sup>

Under these reaction conditions, three acetoxy groups in compound **2** are hydrolyzed stepwise, and phloroglucinol diacetate is formed initially. Phloroglucinol diacetate gives only *O*-benzylated product by successive benzylation because of its relatively low aromatic electron-density. Such hydrolysis and benzylation finally lead to the regiospecific formation of *O*-benzylated product **3**.

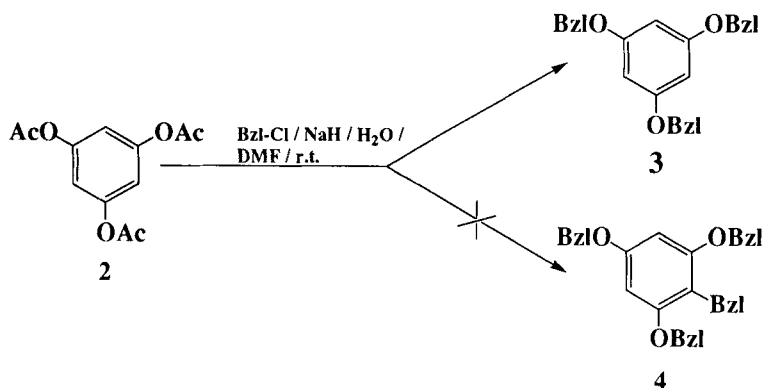


FIG. 1

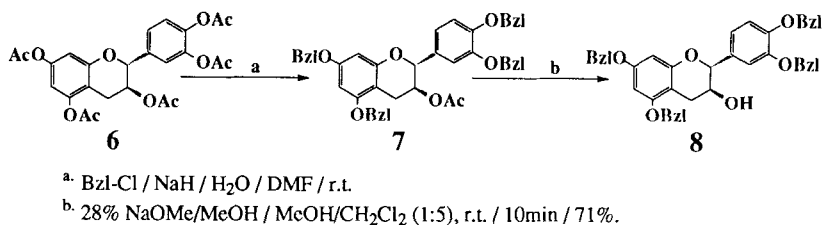


FIG. 2

This method is applicable to other phenols having phloroglucinol-type aromatic ring. For example, (+)-catechin (**5**) was successfully benzylated by this method to give catechin tetrabenzyl ether (**8**) as colorless crystals in overall yield of 71% from compound **5** (FIG. 2). By direct benzylation of compound **5**, C-benzylated product from compound **5** leads to the low yield of compound **8** (46%) and tedious procedure for separation.

### Experimental

To a mixture of compound **2** (1.0 g, 3.97 mmol), benzyl chloride (1.65 ml, 14.3 mmol), 60% NaH in mineral oil (1.14 g, 28.6 mmol) and DMF (20 ml), H<sub>2</sub>O (214  $\mu$ l, 11.9 mmol) was added at 0°C dropwise over a period of 10 minutes. After stirring for 2 h at room temperature, reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated *in vacuo* to yield a yellow oil. Phloroglucinol tribenzyl ether (**3**) was crystallized from methanol as colorless crystals (1.51 g, 97% yield).

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