

# Organic base catalyzed *O*-alkylation of phenols under solvent-free condition

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## Abstract

Several phenyl ethers were prepared under solvent-free condition at room temperature with good to excellent yields by simply grinding the mixture of relevant phenol, alkyl bromide, anhydrous potassium carbonate and organic base as catalyst in a mortar. This method is easy to handle and provides also a convenient procedure for protecting phenols in organic synthesis.

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## 1. Introduction

Solid-state reaction is a green reaction and can be accelerated by heating, shaking, grinding of the reaction mixture and irradiation with ultrasound, which makes it a much ideal synthetic process. And it can avoid the environmental pollution, toxicity and flammability caused by solvents, and has been successfully applied to many kinds of reactions [1–6]. Hence, the investigation of solid-state reaction attracts much attention in recent decades [7,8]. The traditional methods for synthesis of phenyl ethers suffer a rigorous condition such as the strong base and high temperature via Williamson reaction [9–11]. Although a wide variety of procedures has been developed to prepare ethers, including the use of crown ethers [12,13], phase-transfer catalysis [14–16], ionic liquids [17,18], and microwave method and so on [19–24], few examples have been presented using solid-state reaction [25–27]. In this paper, we describe a very simple and convenient method to synthesize the phenyl ethers via the *O*-alkylation/etherification of phenols under solvent-free condition.

## 2. Experimental

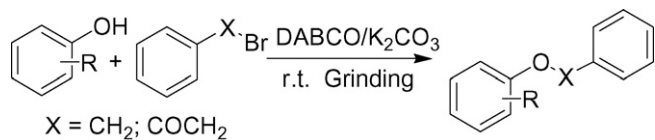
### 2.1. Materials and facilities

All melting points were determined on a XT-4 melting point apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured with Bruker AM-400 spectrometer using CDCl<sub>3</sub> as a solvent and TMS as an internal standard. Elemental analyses were determined with a Carioel elemental analyzer. MS spectra were measured with a ZAB-HS spectrometer. All phenols and other chemicals were purchased from Aldrich without further purification.

### 2.2. General procedure for synthesis of phenol ethers

The corresponding phenols (5 mmol), anhydrous K<sub>2</sub>CO<sub>3</sub> (6.5 mmol), organic base (0.125 mmol) and alkyl bromides (5 mmol) were mixed in a mortar and grinded intermittently using a pestle. The mixture changed to mushy state within a proper reaction time and then solidified itself. TLC monitored the reaction. Once the reaction was completed, the crude products were purified by silica gel chromatography using hexane/ethyl acetate as eluent. All obtained compounds have been characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS (FAB), and elemental analysis. The data are consistent with literatures.

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Scheme 1. *O*-Alkylation of phenols under solvent-free condition.

### 3. Results and discussion

The alkylation reaction is an important transformation in organic synthesis whereas generally involving a rigorous condition such as the strong base and high temperature. Recently, we noticed that the *O*-alkylation reaction of phenols with *tert*-butyl halide could be easily carried out in the presence of liquid amines [28]. Hereby, we envisioned that organic bases, for example 1,4-diazabicyclo[2,2,2] octane (DABCO), would be efficient catalysts for the *O*-alkylation of phenols. Out of our expectation, the etherification reaction of phenols with phenacyl bromide was failed to be carried out under refluxed condition using DABCO as catalyst in THF or acetonitrile. Dramatically, this catalytic reaction took place very well in solid state at room temperature (Scheme 1).

#### 3.1. The *O*-alkylation of phenols with phenacyl bromide

##### 3.1.1. Synthesis of phenacyl ethers

The phenacyl bromide was firstly chosen as *O*-alkylation reagent. Then the mixture of phenol, phenacyl bromide, DABCO and anhydrous K<sub>2</sub>CO<sub>3</sub> was grinded in a mortar. It was found that a new substance appeared several minutes later with the disappearance of reactants upon TLC plate. Other inorganic bases such as anhydrous Na<sub>2</sub>CO<sub>3</sub>, NaOH, and KOH having less activity can also be used in this reaction instead of anhydrous K<sub>2</sub>CO<sub>3</sub>. To further extend the scope of the reaction, several other substituted phenols were utilized as substrates in the reaction with phenacyl bromide in the presence of DABCO (Table 1).

These experimental results exhibit that all investigated phenols can be smoothly converted to the corresponding ethers with excellent yield except for 4-nitrophenol which might be attributed to lower electron density of Nu<sup>-</sup> (hydroxyl).

##### 3.1.2. Characterization of new phenacyl ethers

**3.1.2.1. *p*-*tert*-Butylphenyl phenacyl ether (2A).** A white crystal; mp 67–68 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 8.03 (dd, *J*<sub>1</sub> = 1.5 Hz, *J*<sub>2</sub> = 8.7 Hz, 2H), 7.63–7.48 (m, 3H), 7.34–7.25 (m, 2H), 6.93–6.81 (m, 2H), 5.27 (s, 2H), 1.32 (s, 9H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 194.82, 155.67, 134.48, 133.78, 128.74, 128.09, 126.27, 114.76, 114.20, 70.80, 34.00, 31.39. MS (FAB): *m/z* [M]<sup>+</sup> calcd for C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>: 268.3; found: 268.1. Anal. Calcd for C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>: C, 80.55; H, 7.52. Found: C, 80.23; H, 7.19.

**3.1.2.2. 5,7-Dibromo-8-phenacyloxyquinoline (5A).** A white crystal; mp 119–120 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 8.78 (d, *J* = 3.6 Hz, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 8.05–8.01 (m, 4H), 7.61–7.46 (m, 4H), 5.85 (s, 2H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ = 193.95, 150.92, 150.18, 149.69, 141.63, 135.59, 135.28, 134.38, 133.44, 133.07, 128.72, 127.75, 127.23, 123.53,

Table 1  
*O*-Alkylation of phenols with phenacyl bromide

Entry	Phenol	Time (min)	Yield <sup>a</sup> (%)	Conversion (%)
1		8	88	100
2		7	>99	100
3		6	99	100
4		9	94	100
5		10	96	100
6		9	99	100
7		8	>99	100
8		9	94	100
9		12	91	100
10		60	NR	NR

<sup>a</sup> Isolated yield.

123.20, 114.56, 114.23, 75.79. MS (FAB): *m/z* [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>11</sub>Br<sub>2</sub>NO<sub>2</sub>: 422.1; found: 422.0. Anal. Calcd for C<sub>17</sub>H<sub>11</sub>Br<sub>2</sub>NO<sub>2</sub>: C, 48.70; H, 2.65; N, 3.34. Found: C, 48.89; H, 2.46; N, 2.97.

**3.1.2.3. 3-Methoxy-2-phenacyloxybenzaldehyde (6A).** A white crystal; mp 84.5–85 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 10.65 (s, 1H), 7.91 (dd, *J*<sub>1</sub> = 2.4 Hz, *J*<sub>2</sub> = 8.4 Hz, 2H), 7.61–7.42 (m, 4H), 7.26–7.11 (m, 2H), 5.50 (s, 2H), 3.84 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 194.34, 190.46, 151.84, 150.41, 134.47, 133.66, 129.69, 128.75, 127.70, 124.09, 119.32, 117.99, 74.78, 56.05. MS (FAB): *m/z* [M]<sup>+</sup> calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>: 271.3; found: 271.1. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>: C, 71.09; H, 5.22. Found: C, 71.24; H, 4.84.

**3.1.2.4. 3-Methoxy-4-phenacyloxybenzaldehyde (8A).** A white crystal; mp 121–122 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 9.84 (s, 1H), 8.02–7.99 (m, 2H), 7.67–7.28 (m, 5H), 6.86 (d, *J* = 8.4 Hz, 1 H), 5.50 (s, 2H), 3.96 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 193.03, 190.84, 152.68, 149.84, 134.13, 130.85, 128.91, 127.92, 126.19, 112.41, 109.66, 71.05, 56.01. MS (FAB): *m/z* [M]<sup>+</sup> calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>: 271.3; found: 271.2 (M<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>: C, 71.09; H, 5.22. Found: C, 70.76; H, 5.07.

#### 3.2. The effect of organic base on the synthesis of 4-methoxyphenylphenacyl ether

The scope of the reaction was then investigated by using the 4-methoxyphenol as substrate with various organic bases. These

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