Microwave Mediated Protection of Hindered Phenols and Alcohols

Tejas Pothi, Mahesh Dawange, Kamlesh Chavan, Rajiv Sharma, and Nabajyoti Deka*

Department of Medicinal Chemistry, Piramal Healthcare Limited, 1-Nirlon Complex, Off Western Express Highway, Goregaon (E), Mumbai 400 063, India. *E-mail: nabajyoti.deka@piramal.com
(Received August 12, 2012; Accepted September 14, 2012)

ABSTRACT. Hindered phenols and alcohols were protected as their corresponding ethers using different alkylating agents in presence of KOH/DMSO under microwave irradiation.

\[
\text{R}^\text{II} \text{OH} \xrightarrow{\text{KOH/DMSO}} \text{R}'\text{X}, \text{ MW} \xrightarrow{10-15 \text{ Mins}, 80\%-90\% \text{ Yield}} \text{R}^\text{II} \text{OR}'
\]

Key words: Microwave, Alkylation, Hindered phenols, Alkyl ether, Etherification

INTRODUCTION

Alcohols and phenols are important class of compounds whose versatility allows their application in several fields of the chemical and pharmaceutical industries. Protection of the hydroxyl group as its alkylated derivatives is very important reaction in organic synthesis. A wide variety of procedures for the protection of alcohols and phenols to corresponding ethers have been developed during the last centuries.1-5 Among them, the common methods for the conversion of alcohols to ethers are based on the reaction of metal salts of alcohols with different alkylating agents. The popular and general method of etherification, Williamson’s Ether Synthesis6 was discovered in 1850, which has limitation for tertiary alcohols. It is satisfactory only for primary alcohols and poor yields were obtained for secondary alcohols.7 For improvement of Williamson’s procedure, use of phase transfer catalyst was also reported.8 Condensation of alcohols or their salts with aldehydes,9 olefines,10 alkyl oxides11 and dialkyl phosphite12 under acidic or basic conditions are also reported for ether synthesis. The direct alkylation of alcohols or phenols in to ethers by using diazomethane or diazoalkane does not involve the formation of phenoxide or alkoxide ion and limited to methyl ethers only. Etherification of alcohols also carried out with orthocarbonate ester,13 dialkyl oxalate ester,14 onium salt15 and using dicyclohexylcarbodiimide.16 However none of these methodologies are applicable for tertiary alcohols and suffer from highly basic or acidic conditions.

The use of Cerium (IV) Ammonium Nitrate (CAN) as catalyst for ether synthesis by alcoholyzes of allylic and tertiary benzylic alcohols is reported.17 But in this procedure also the alcoholysis is reported only for primary, secondary and tertiary benzylic hydroxyl groups.

Here we report a very convenient and efficient general method for the protection of hindered phenols and alcohols using microwave irradiation. Most microwave protocols developed for the preparation of aliphatic ethers involve a large excess of base to deprotonate the poorly acidic alcohol group. Phenols are more acidic than aliphatic alcohols, and therefore a milder base can be applied to bring about the reaction. Under thermal conditions, use of mild bases was occasionally reported, but these reactions often suffer from long reaction times (up to 72 h)18 and less efficient for hindered phenols and alcohols. Almost all protocols described for alkylation of phenols using mild base under microwave irradiation employ a large excess of bases.19 Under classical heating the alkylation reagent may undergoes degradation reaction to the corresponding alcohol. Therefore these reactions are often run as a two-step process with pre-formation of the phenoxide salt and subsequent addition of the alkyl halide. In our attempts to extend the application range of microwave-assisted methods to protect phenols and alcohols as their alkyl ether, we have found that hindered phenols and alcohols can be alkylated under microwave conditions in the presence of KOH in DMSO using different alkylating agent. The reactions proceed efficiently in high yield at 100 °C within a few minutes. Rate of the reaction enhanced significantly over the conventional heating method.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used as received. The alkylating agents
was irradiated at 100 °C and a maximum operating pressure of 200 psi. But pressure was not monitored during the experiments. A Bruker 300 MHz instrument equipped with a 5 mm H/13C/X (BBO) probe and the solvent indicated with tetramethylsilane as an internal standard, unless otherwise stated. The data obtained so, were processed and analyzed by using Bruker software, XWIN NMR version 3.5. HRMS results were obtained on ‘ESI-QTOF’ instruments of Bruker Daltonics (model MicrotofQ). 5 µl of each sample (10 µg per ml) was injected. The sample was ionized using Electron Spray Ionisation technique. The data obtained so, were processed and analyzed by using software Hystar3.2 s/w. Automated column chromatography was performed on a CombiFlash Rf 200 (Teledyne Isco Inc.).

A Typical Procedure for the Protection of Hindered Phenols and Alcohols

In a 10 mL of Microwave vial 1 mmol of the phenol or alcohol was placed and dissolved in 2/3 ml of DMSO. Two equivalent of KOH (pallet) was added to it and stirred to make a clear solution. To the clear solution, two equivalents of alkyl halide was added and the reaction mixture was irradiated at 100 °C in MW (CEM Discover) for 8/10 min. The reaction was monitored by TLC. Vaughn’s reagent [prepared by mixing 4.8 g of (NH4)6Mo7O24·4H2O and 0.2 g of Ce(SO4)3 in 100 ml of a 3.5 N H2SO4 solution] was used as spraying reagent for UV negative compounds. After completion, the reaction was diluted with water and extracted with ethyl acetate. Organic layer was washed with brine solution, dried over sodium sulphate and distilled under vacuum to yielded crude O-alkylated product. The crude product was purified by using ethyl acetate and pet-ether solvent system in automated Rf-200 flash column chromatography and characterized by spectral analysis. Analytical data of synthesized compounds are available as supplementary data.

Experimental and Analytical Data

All reagents and solvents were obtained from commercial sources and used as received. The alkylation agents (Methyl iodide, Ethyl iodide, n-heptyl bromide and 2-chloroethanol) were purchased from Sigma Aldrich. All microwave irradiation experiments described herein were performed using a single-mode Discover Labmate System from CEM Corp. using standard Pyrex or quartz vessels (capacity 10 mL). Experiments were performed in temperature-control mode where the temperature was controlled using the built-in calibrated IR sensor. It has a maximum operating temperature of 200 °C and a maximum operating pressure of 200 psi. But pressure was not monitored during the experiments. 1H NMR spectra were obtained on a ‘Bruker 300 MHz’ instrument equipped with a 5 mm H/13C/X (BBO) probe and the solvent indicated with tetramethylsilane as an internal standard. The data obtained so, were processed and analyzed by using Bruker software, XWIN NMR version 3.5.

Analytical HPLC was run using a Zorbax Eclipse XDB-C8 3.5 µm 4.6×75 mm column eluting with a mixture of acetonitrile and water containing 0.1% trifluoroacetic acid with a 5 minute gradient of 10–100%.

HRMS results were obtained on ‘ESI-QTOF’ instruments of Bruker Daltonics (model MicrotofQ). 5 µl of each sample (10 µg per ml) was injected. The sample was ionized using Electron Spray Ionisation technique. The data obtained so, were processed and analyzed by using software Hystar3.2 s/w. Automated column chromatography was performed on a CombiFlash Rf 200 (Teledyne Isco Inc.).

A Typical Procedure for the Microwave Mediated Protection of Hindered Phenols and Alcohols

In a 10 ml of Microwave vial 1 mmol of the phenol or alcohol was placed and dissolved in 2/3 ml of DMSO. Two equivalent of KOH (pallet) was added to it and stirred to make a clear solution. To the clear solution, two equivalents of alkyl halide was added and the reaction mixture was irradiated at 100 °C in MW (CEM Discover) for 8/10 mins. The reaction was monitored by TLC. Vaughn’s reagent [prepared by mixing 4.8 g of (NH4)6Mo7O24·4H2O and 0.2 g of Ce(SO4)3 in 100 ml of a 3.5 N H2SO4 solution] was used as spraying reagent for UV negative compounds. After completion, the reaction was diluted with water and extracted with ethyl acetate. Organic layer was washed with brine solution, dried over sodium sulphate and distilled under vacuum to yielded crude O-alkylated product. The crude product was purified by using ethyl acetate and pet-ether solvent system in automated Rf-200 flash column chromatography and characterized by spectral analysis.
Analytical Data
1,3-di-tert-butyl-2-methoxy-5-methylbenzene [1a]
1H NMR (300 MHz, CDCl3) δ: 1.25 (s, 18H), 3.69 (s, 3H), 7.06 (s, 2H). HRMS (m/z): [M]+ cale for C19H23O, 234.1984; found, 234.1987.

1,3-di-tert-butyl-2-ethoxy-5-methylbenzene [1b]
1H NMR (300 MHz, CDCl3) δ: 0.68 (t, J=6.9 Hz, 3H), 1.25 (s, 18H), 2.3 (s, 3H), 4.03 (q, J=6.9 Hz, 2H), 7.06 (s, 2H). HRMS (m/z): [M]+ cale for C19H23O, 248.2140; found, 248.2139.

1,3-di-tert-butyl-2-(heptyloxy)-5-methylbenzene [1c]
1H NMR (300 MHz, CDCl3) δ: 0.86 (t, J=6.9 Hz, 3H), 1.21 (s, 18H), 1.30–1.33 (m, 6H), 1.48 (m, 2H), 1.73 (m, 2H), 2.33 (s, 3H), 4.11 (t, J=6.9 Hz, 2H), 7.08 (s, 2H). HRMS (m/z): [M]+ cale for C22H29O, 318.2923; found, 318.2918.

2-(2,6-di-tert-butylphenoxy)ethanol [1d]
1H NMR (300 MHz, CDCl3) δ: 1.21 (s, 18H), 2.3 (s, 3H), 3.69 (m, 2H), 3.98 (m, 2H), 7.06 (s, 2H). HRMS (m/z): [M]+ cale for C13H19O2, 264.2089; found, 264.2091; m/z: 264.40.

1,3-diisopropyl-2-methoxybenzene [2a]
1H NMR (300 MHz, CDCl3) δ: 1.19 (s, 12H), 3.22 (m, 2H), 3.91 (s, 3H), 7.14 (t, J=7.2Hz, 1H), 7.30 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C13H19O, 192.1514; found, 192.1521.

2-ethoxy-1,3-diisopropylbenzene [2b]
1H NMR (300 MHz, CDCl3) δ: 1.20 (s, 12H), 1.35 (t, J=6.6Hz, 3H), 3.18 (m, 2H), 4.15 (q, J=6.6Hz, 2H), 7.17 (t, J=7.2Hz, 1H), 7.32 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C13H19O, 206.3239; found, 206.3219.

2-(heptyloxy)-1,3-diisopropylbenzene [2c]
1H NMR (300 MHz, CDCl3) δ: 1.12 (m, 3H), 1.21 (s, 12H), 1.32–1.39 (m, 6H), 1.51–1.70 (m, 4H), 3.17 (m, 2H), 4.15 (m, 2H), 7.16 (t, J=7.2Hz, 1H), 7.30 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C19H23O, 276.4568; found, 276.4547.

2-(2,6-diisoproplyphenoxy)ethanol [2d]
1H NMR (300 MHz, CDCl3) δ: 1.25 (s, 12H), 3.17 (m, 2H), 3.70 (brs, 1H), 3.73 (m, 2H), 4.38 (m, 2H), 7.15 (t, J=7.2Hz, 1H), 7.29 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C14H27O2, 222.3233; found, 222.3227.

1,3-di-tert-butyl-2-methoxybenzene [3a]
1H NMR (300 MHz, CDCl3) δ: 1.32 (s, 18H), 3.94 (s, 3H), 7.12 (t, J=7.2Hz, 1H), 7.21 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C19H23O, 220.1827; found, 220.1819.

1,3-di-tert-butyl-2-ethoxybenzene [3b]
1H NMR (300 MHz, CDCl3) δ: 1.29 (t, J=6.6Hz, 3H), 1.33 (s, 18H), 4.12 (q, J=6.6Hz, 2H), 7.12 (t, J=7.2Hz, 1H), 7.22 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C13H19O, 234.1984; found, 234.1979.

1,3-di-tert-butyl-2-(heptyloxy)benzene [3c]
1H NMR (300 MHz, CDCl3) δ: 1.12 (m, 3H), 1.25–1.31 (m, 6H), 1.33 (s, 18H), 1.45 (m, 2H), 1.76 (m, 2H), 4.12 (m, 2H), 7.12 (t, J=7.2Hz, 1H), 7.21 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C21H35O, 304.2766; found, 304.2761.

2-(2,6-di-tert-butylphenoxy)ethanol [3d]
1H NMR (300 MHz, CDCl3) δ: 1.34 (s, 18H), 3.67 (brs, 1H), 3.71 (m, 2H), 4.36 (m, 2H), 7.14 (t, J=7.2Hz, 1H), 7.27 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C19H25O2, 250.1933; found, 250.1929.

2-methoxy-1,3-dimethylbenzene [4a]
1H NMR (300 MHz, CDCl3) δ: 2.18 (s, 6H), 3.85 (s, 3H), 6.91 (t, J=7.8Hz, 1H), 6.98 (d, J=7.8Hz, 2H). HRMS (m/z): [M]+ cale for C10H16O, 136.0888; found, 136.0891.

2-methoxy-1,3-dimethylbenzene [4b]
1H NMR (300 MHz, CDCl3) δ: 1.30 (t, J=6.9Hz, 3H), 2.18 (s, 6H), 4.11 (q, J=6.9Hz, 2H), 6.90 (t, J=7.8Hz, 1H), 6.98 (d, J=7.8Hz, 2H). HRMS (m/z): [M]+ cale for C10H16O, 150.1045; found, 150.1048.

2-(heptyloxy)-1,3-dimethylbenzene [4c]
1H NMR (300 MHz, CDCl3) δ: 1.18 (t, J=6.9Hz, 3H), 1.21–1.30 (m, 6H), 2.17 (s, 6H), 4.15–1.77 (m, 4H), 4.11 (m, 2H), 7.12 (t, J=7.2Hz, 1H), 7.21 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C13H19O, 220.1827; found, 220.1829.

2-(2,6-dimethylphenoxy)ethanol [4d]
1H NMR (300 MHz, CDCl3) δ: 2.18 (s, 6H), 3.66 (brs, 1H), 3.71 (m, 2H), 4.35 (m, 2H), 7.13 (t, J=7.2Hz, 1H), 7.27 (d, J=7.2Hz, 2H). HRMS (m/z): [M]+ cale for C16H20O2, 166.0994; found, 166.0989.

1-methoxy-1-methyleclohexane [5a]
1H NMR (300 MHz, CDCl3) δ: 1.31 (s, 3H), 1.41–1.45...
709

Microwave Mediated Protection of Hindered Phenols and Alcohols

(1-methylcyclohexane [5b]

1 H NMR (300 MHz, CDCl₃) δ: 1.11 (t, J=6.6Hz, 3H), 1.30 (s, 3H), 1.21–1.30 (m, 6H), 1.45–1.77 (m, 4H), 4.11 (m, 2H), 7.49 (m, 3H), 7.59 (d, J=7 Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₁H₁₀F₆O₂, 272.0636; found, 272.0632; m/z: 272.06.

(1,1,3,3,3-hexafluoropropan-2-yl)benzene [7b]

1 H NMR (300 MHz, CDCl₃) δ: 1.35 (t, J=6.9Hz, 3H), 3.64 (q, J=6.9Hz, 2H), 7.49 (m, 3H), 7.59 (d, J=7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₁H₁₀F₆O₂, 272.0636; found, 272.0632; m/z: 272.06.

(1,1,3,3,3-hexafluoro-2-(heptyloxy)propan-2-yl)benzene [7c]

1 H NMR (300 MHz, CDCl₃): 0.91 (t, J=6.9Hz, 3H), 1.21–1.30 (m, 6H), 1.45–1.77 (m, 4H), 4.11 (m, 2H), 7.49 (m, 3H), 7.59 (d, J=7 Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₁H₁₀F₆O₂, 342.1418; found, 342.1421.

2-((1-methylcyclohexyl)oxy)ethanol [5d]

1 H NMR (300 MHz, CDCl₃): 0.9 (t, J=6.9Hz, 3H), 1.76 (m, 4H), 4.11 (m, 2H), 6.90 (d, J=8.7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₂H₂₀O₂, 288.0585; found, 288.0577.

1-bromo-4-methoxybenzene [8a]

1 H NMR (300 MHz, DMSO-d₆) δ: 3.74 (s, 3H), 6.92 (d, J=8.7Hz, 2H), 7.46 (d, J=8.7Hz, 2H), 185.9680; found, 185.9676.

1-bromo-4-ethoxybenzene [8b]

1 H NMR (300 MHz, DMSO-d₆) δ: 1.33 (t, 3H), 4.03 (q, J=13Hz, 2H), 6.90 (d, J=8.7Hz, 2H), 7.44 (d, J=8.7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₂H₁₂BrO, 199.9837; found, 199.9839.

1-bromo-4-(heptyloxy)benzene [8c]

1 H NMR (300 MHz, DMSO-d₆) δ: 0.86 (t, J=6.9Hz, 3H), 1.21–1.31 (m, 6H), 1.45–1.76 (m, 4H), 4.11 (m, 2H), 6.90 (d, J=8.7Hz, 2H), 7.43 (d, J=8.7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₃H₁₃BrO, 270.0619; found, 270.0621.

2-(4-bromophenoxy)ethanol [8d]

1 H NMR (300 MHz, DMSO-d₆) δ: 3.69 (m, J=4.5Hz, 2H), 3.98 (t, J=4.5Hz, 2H), 4.87 (brs, 1H), 6.90 (d, J=8.7Hz, 2H), 7.45 (d, J=8.7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₃H₁₂BrO, 215.9786; found, 215.9779.

2-(4-bromophenoxy)ethanol [Byproduct-Entry 8d]

1 H NMR, (300 MHz, DMSO-d₆) δ: 3.49 (m, 4H), 3.74 (m, 2H), 4.0 (m, 2H), 4.61 (brs, 1H), 6.93 (d, J=8.7Hz, 2H), 7.43 (d, J=8.7Hz, 2H). HRMS (m/z): [M⁺] coted for C₁₀H₁₀BrO₂, 260.0048; found, 260.0053.
RESULT AND DISCUSSION

In connection to our medicinal chemistry program to synthesize building blocks having different aryl alkyl ether unit for SAR study, we needed to prepare alkyl ethers of hindered phenols and alcohols. For rapid synthesis of alkyl ethers of hindered phenols we explored microwave irradiation as a source of energy. A number of reactions were carried out with different phenols and alcohols (Table 1). It is a convenient method for the synthesis of different alkyl aryl ether of corresponding hindered phenols using different alkylating agent.

Table 1. Etherification of hindered phenols and alcohols with different alkylating agent

<table>
<thead>
<tr>
<th>Entry</th>
<th>R−OH</th>
<th>R−OR′</th>
<th>Time (min) / Temp (ºC)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a. 10 / 100 ºC</td>
<td>a. OR′</td>
<td>a. 10 / 100 ºC</td>
<td>a. 80</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 100 ºC</td>
<td>b. OR′</td>
<td>b. 10 / 100 ºC</td>
<td>b. 82</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 100 ºC</td>
<td>c. OR′</td>
<td>c. 10 / 100 ºC</td>
<td>c. 85</td>
</tr>
<tr>
<td></td>
<td>d. 12 / 100 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 100 ºC</td>
<td>d. 80</td>
</tr>
<tr>
<td>2</td>
<td>a. 10 / 100 ºC</td>
<td>a. OR′</td>
<td>a. 10 / 100 ºC</td>
<td>a. 75</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 100 ºC</td>
<td>b. OR′</td>
<td>b. 10 / 100 ºC</td>
<td>b. 80</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 100 ºC</td>
<td>c. OR′</td>
<td>c. 10 / 100 ºC</td>
<td>c. 78</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 100 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 100 ºC</td>
<td>d. 76</td>
</tr>
<tr>
<td>3</td>
<td>a. 10 / 100 ºC</td>
<td>a. OR′</td>
<td>a. 10 / 100 ºC</td>
<td>a. 80</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 100 ºC</td>
<td>b. OR′</td>
<td>b. 10 / 100 ºC</td>
<td>b. 80</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 100 ºC</td>
<td>c. OR′</td>
<td>c. 10 / 100 ºC</td>
<td>c. 85</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 100 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 100 ºC</td>
<td>d. 80</td>
</tr>
<tr>
<td>4</td>
<td>a. 10 / 80 ºC</td>
<td>a. OR′</td>
<td>a. 10 / 80 ºC</td>
<td>a. 75</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 80 ºC</td>
<td>b. OR′</td>
<td>b. 10 / 80 ºC</td>
<td>b. 78</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 80 ºC</td>
<td>c. OR′</td>
<td>c. 10 / 80 ºC</td>
<td>c. 85</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 80 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 80 ºC</td>
<td>d. 80</td>
</tr>
<tr>
<td>5</td>
<td>a. 10 / 80 ºC</td>
<td>a. OR′</td>
<td>a. 10 / 80 ºC</td>
<td>a. 72</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 80 ºC</td>
<td>b. OR′</td>
<td>b. 10 / 80 ºC</td>
<td>b. 75</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 80 ºC</td>
<td>c. OR′</td>
<td>c. 10 / 80 ºC</td>
<td>c. 80</td>
</tr>
<tr>
<td></td>
<td>d. 15 / 80 ºC</td>
<td>d. OR′</td>
<td>d. 15 / 80 ºC</td>
<td>d. 75</td>
</tr>
<tr>
<td>6</td>
<td>a. 08 / 80 ºC</td>
<td>a. OR′</td>
<td>a. 08 / 80 ºC</td>
<td>a. 80</td>
</tr>
<tr>
<td></td>
<td>b. 08 / 80 ºC</td>
<td>b. OR′</td>
<td>b. 08 / 80 ºC</td>
<td>b. 80</td>
</tr>
<tr>
<td></td>
<td>c. 08 / 80 ºC</td>
<td>c. OR′</td>
<td>c. 08 / 80 ºC</td>
<td>c. 85</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 80 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 80 ºC</td>
<td>d. 75</td>
</tr>
<tr>
<td>7</td>
<td>a. 08 / 80 ºC</td>
<td>a. OR′</td>
<td>a. 08 / 80 ºC</td>
<td>a. 80</td>
</tr>
<tr>
<td></td>
<td>b. 08 / 80 ºC</td>
<td>b. OR′</td>
<td>b. 08 / 80 ºC</td>
<td>b. 85</td>
</tr>
<tr>
<td></td>
<td>c. 08 / 80 ºC</td>
<td>c. OR′</td>
<td>c. 08 / 80 ºC</td>
<td>c. 88</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 80 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 80 ºC</td>
<td>d. 75</td>
</tr>
<tr>
<td>8</td>
<td>a. 08 / 80 ºC</td>
<td>a. OR′</td>
<td>a. 08 / 80 ºC</td>
<td>a. 82</td>
</tr>
<tr>
<td></td>
<td>b. 08 / 80 ºC</td>
<td>b. OR′</td>
<td>b. 08 / 80 ºC</td>
<td>b. 85</td>
</tr>
<tr>
<td></td>
<td>c. 05 / 80 ºC</td>
<td>c. OR′</td>
<td>c. 05 / 80 ºC</td>
<td>c. 80</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 80 ºC</td>
<td>d. OR′</td>
<td>d. 10 / 80 ºC</td>
<td>d. 68</td>
</tr>
<tr>
<td>9</td>
<td>a. 10 / 100ºC</td>
<td>a. No Required Product</td>
<td>a. 10 / 100ºC</td>
<td>a. NA</td>
</tr>
<tr>
<td></td>
<td>b. 10 / 100ºC</td>
<td>b. No Required Product</td>
<td>b. 10 / 100ºC</td>
<td>b. NA</td>
</tr>
<tr>
<td></td>
<td>c. 10 / 100ºC</td>
<td>c. No Required Product</td>
<td>c. 10 / 100ºC</td>
<td>c. NA</td>
</tr>
<tr>
<td></td>
<td>d. 10 / 100ºC</td>
<td>d. No Required Product</td>
<td>d. 10 / 100ºC</td>
<td>d. NA</td>
</tr>
</tbody>
</table>

(a) Where R′−X=CH₃−I. (b) Where R′−X=C₃H₇−I. (c) Where R′−X=1-bromoheptane. (d) Where R′−X=2-chloroethanol.
Here we observed that the kinetics of the reaction not only depend on the acidic nature of the hydroxyl proton (pKₐ at the –OH) but also on the steric hindrance. For the greater steric hindrance the rate of reaction was slower. When 2,6-di-tert-butyl-4-methylphenol was treated with 1-bromohexane, it took 15 minutes at 100 °C (Entry 1c) whereas 4-bromo phenol took 5 mins at 80 °C (Entry 8c). In this case, the field effect (+I effect and –I effect) also played a significant role. In case of 2,6-di-tert-butyl-4-methylphenol, two tert-butyl groups at ortho positions and one methyl at para position are contributing towards +I effect whereas in case of 4-bromo phenol the Br at para position is contributing towards –I effect. Thus 4-bromo phenol is more acidic (and no steric hindrance) compared to 2,6-di-tert-butyl-4-methylphenol.

The formation of 1-bromo-4-(heptyloxy)benzene was completed within 2 hours at room temperature but etherification of 2,6-di-tert-butyl-4-methylphenol did not take place at room temperature even after stirring for 15 hours. Initially we carried out the microwave reactions at 80 °C and irradiated for 10 minutes. But O-alkylation of 2,6-di-tert-butyl-4-methylphenol (entry 1), 2,6-diisopropylphenol (entry 2) and 2,6-di-tert-butylphenol (entry 3) were not completed and hence we increased the reaction temperature keeping the reaction time constant (10 Minutes). Due to the presence of –CF₃ group, 2,2,2-trifluoro-1,1-diphenylethanol (entry 6) and 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (entry 7), are more acidic nature and the reactions were completed in 8 minutes. The –OH group of 1,1-diphenylethanol is less hindered and also less acidic in nature compared to 2,2,2-trifluoro-1,1-diphenylethanol. Reaction of 1,1-diphenylethanol with alkyl halides (a-d) at higher temperature exhibited elimination reaction to afforded ethene-1,1-diylidibenzene as major product (Entry 9). Reaction of 2,2,2-trifluoro-1,1-diphenylethanol with alkyl halides (a-d) afforded corresponding ethers in quantitative yields (Entry 6). For the same reason reaction of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (Entry 7) afforded its alkylated products within shorter reaction time and lower temperature. Protection of 4-bromophenol with 2-chloro ethanol (Entry 8d) using same reaction condition afforded 2-(2-(4-bromophenoxo)ethoxy)ethanol as a byproduct. But the –OH group of 4-bromo phenol is more acidic in nature compared to the –OH attached to chloroethyl (–CH₂CH₂Cl) and we observed the formation of expected O-alkylated product of 4-bromo phenol.

CONCLUSION

In summary, herein we report an efficient and practical application of microwave mediated etherification of hindered phenols and alcohols. This method is useful and one can use different alkyl halides (R'–X) to prepare different ethers from hindered phenols as well as from tertiary alcohols.

Acknowledgments. We thank the Department of Analytical Chemistry for providing us with NMR and Mass data.

REFERENCES

9. (d) Zupancie, B. G; Sopiec, M. Synthesis 1979, 123.