# Microwave Mediated Protection of Hindered Phenols and Alcohols

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

$$R-OH \xrightarrow[\text{10-15 Mins, 80\% - 90\% Yield}]{\text{KOH/DMSO, R'}-\text{X, MW}} R^{\nearrow O}\searrow R'$$
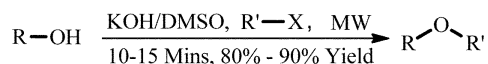
Key words: Microwave, Alkylation, Hindered phenols, Alkyl ether, Etherification

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 Synthesis[6] 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 oxides[11] and dialkyl phosphite[12] 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 salt[15] 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 alcoholyses 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.[17] 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 alkylating 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 precede efficiently in high yield at 100 ºC 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

(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 ºC and a maximum operating pressure of 200 psi. But pressure was not monitored during the experiments. ^{1}H NMR spectra were obtained on a 'Bruker 300 MHz' instrument equipped with a 5 mm ^{1}H/^{13}C/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 equivalent of alkyl halide was added and the reaction mixture was irradiated at 100 ºC in MW (CEM Discover) for 8/10 min. The reaction was monitored by TLC. Vaughn's reagent [prepared by mixing 4.8 g of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 ml of a 3.5 N H_2SO_4 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 alkylating 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 ºC and a maximum operating pressure of 200 psi. But pressure was not monitored during the experiments.

^{1}H NMR spectra were obtained on a 'Bruker 300 MHz' instrument equipped with a 5 mm ^{1}H/^{13}C/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 equivalent of alkyl halide was added and the reaction mixture was irradiated at 100 ºC in MW (CEM Discover) for 8/10 mins. The reaction was monitored by TLC. Vaughn's reagent [prepared by mixing 4.8 g of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 ml of a 3.5 N H_2SO_4 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]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.25 (s, 18H), 2.30 (s, 3H), 3.69 (s, 3H), 7.06 (s, 2H). HRMS (m/z): [M]$^+$ calcd for C$_{16}$H$_{26}$O, 234.1984; found, 234.1987.

1,3-di-tert-butyl-2-ethoxy-5-methylbenzene [1b]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{17}$H$_{28}$O, 248.2140; found, 248.2139.

1,3-di-tert-butyl-2-(heptyloxy)-5-methylbenzene [1c]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{22}$H$_{38}$O, 318.2923; found, 318.2918.

2-(2,6-di-tert-butyl-4-methylphenoxy)ethanol [1d]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{17}$H$_{28}$O$_2$, 264.2089; found, 264.2091, m/z: 264.40.

1,3-diisopropyl-2-methoxybenzene [2a]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{13}$H$_{20}$O, 192.1514; found, 192.1521.

2-ethoxy-1,3-diisopropylbenzene [2b]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{14}$H$_{22}$O, 206.3239; found, 206.3219.

2-(heptyloxy)-1,3-diisopropylbenzene [2c]

^{1}H NMR (300 MHz, CDCl$_3$) 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=7.2 Hz, 2H). HRMS (m/z): [M]$^+$ calcd for C$_{19}$H$_{32}$O, 276.4568; found, 276.4547.

2-(2,6-diisopropylphenoxy)ethanol [2d]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{14}$H$_{22}$O$_2$, 222.3233; found, 222.3227.

1,3-di-tert-butyl-2-methoxybenzene [3a]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{15}$H$_{24}$O, 220.1827; found, 220.1819.

1,3-di-tert-butyl-2-ethoxybenzene [3b]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{16}$H$_{26}$O, 234.1984; found, 234.1979.

1,3-di-tert-butyl-2-(heptyloxy)benzene [3c]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{21}$H$_{36}$O, 304.2766; found, 304.2761.

2-(2,6-di-tert-butylphenoxy)ethanol [3d]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{16}$H$_{26}$O$_2$, 250.1933; found, 250.1929.

2-methoxy-1,3-dimethylbenzene [4a]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_9$H$_{12}$O, 136.0888; found, 136.0891.

2-methoxy-1,3-dimethylbenzene [4b]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{10}$H$_{14}$O, 150.1045; found, 150.1048.

2-(heptyloxy)-1,3-dimethylbenzene [4c]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.18 (t, J=6.9Hz, 3H), 1.21−1.30 (m, 6H), 2.17 (s, 6H), 1.45−1.77 (m, 4H), 4.11 (m, 2H), 7.12 (t, J=7.2Hz, 1H), 7.21 (d, J=7.2Hz, 2H). HRMS (m/z): [M]$^+$ calcd for C$_{15}$H$_{24}$O, 220.1827; found, 220.1829.

2-(2,6-dimethylphenoxy)ethanol [4d]

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{10}$H$_{14}$O$_2$, 166.0994; found, 166.0989.

1-methoxy-1-methylcyclohexane [5a]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.31 (s, 3H), 1.41−1.45

(m, 4H), 1.48 (m, 2H), 1.56−1.67 (m, 4H), 3.31 (s, 3H). HRMS (*m/z*): [M]$^+$ calcd for C$_8$H$_{16}$O, 128.1201; found, 128.1211.

1-ethoxy-1-methylcyclohexane [5b]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.11 (t, J=6.6Hz, 3H), 1.30 (s, 3H), 1.41−1.47 (m, 4H), 1.52 (m, 2H), 1.58−1.67 (m, 4H), 3.53 (q, J=6.6Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_9$H$_{18}$O, 142.1358; found, 142.1352.

1-(heptyloxy)-1-methylcyclohexane [5c]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.10 (t, J=6.6Hz, 3H), 1.28 (s, 3H), 1.33−1.42 (m, 6H), 1.48−1.57 (m, 12H), 1.67 (m, 2H), 3.43 (m, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_{14}$H$_{28}$O, 212.2140; found, 212.2138.

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

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.30 (s, 3H), 1.41−1.52 (m, 6H), 1.57 (m, 2H), 1.67 (m, 2H), 3.44 (m, 2H), 3.56 (m, 2H), 3.67 (brs, 1H). HRMS (*m/z*): [M]$^+$ calcd for C$_9$H$_{18}$O$_2$, 158.1307; found, 158.1311.

(2,2,2-trifluoro-1-methoxyethane-1,1-diyl)dibenzene [6a]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.3 (s, 3H), 7.36 (m, 6H), 7.42 (m, 4H). HRMS (*m/z*): [M]$^+$ calcd for C$_{15}$H$_{13}$F$_3$O, 266.0918; found, 266.0912.

(1-ethoxy-2,2,2-trifluoroethane-1,1-diyl)dibenzene [6b]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.9 (t, J=6.9Hz, 3H), 4.11 (q, J=6.9Hz, 2H), 7.36 (m, 6H), 7.4 (m, 4H). HRMS (*m/z*): [M]$^+$ calcd for C$_{16}$H$_{15}$F$_3$O, 280.1075; found, 280.1069.

(2,2,2-trifluoro-1-(heptyloxy)ethane-1,1-diyl)dibenzene [6c]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.24 (t, J=13Hz, 3H), 1.21−1.30 (m, 6H), 1.45−1.77 (m, 4H), 4.11 (m, 2H), 7.36 (m, 6H), 7.42 (m, 4H). HRMS (*m/z*): [M]$^+$ calcd for C$_{21}$H$_{25}$F$_3$O, 350.1858; found, 350.1861.

2-(2,2,2-trifluoro-1,1-diphenylethoxy)ethanol [6d]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.48 (m, 2H), 3.57 (m, 2H), 3.65 (brs, 1H), 7.39 (m, 6H), 7.44 (m, 4H). HRMS (*m/z*): [M]$^+$ calcd for C$_{16}$H$_{15}$F$_3$O$_2$, 296.1024; found, 296.1019.

(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)benzene [7a]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.4 (s, 3H), 7.48 (m, 3H), 7.74(d, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_{10}$H$_8$F$_6$O, 258.0479; found, 258.0468.

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

^{1}H NMR (300 MHz, CDCl$_3$) 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]$^+$ calcd for C$_{11}$H$_{10}$F$_6$O, 272.0636; found, 272.0632; m/z: 272.06.

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

^{1}H NMR (300 MHz, CDCl$_3$) δ: 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]$^+$ calcd for C$_{16}$H$_{20}$F$_6$O, 342.1418; found, 342.1421.

2-((1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-yl)oxy)-ethanol [7d]

^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.09 (brs, 1H), 3.74 (m, 2H), 3.8 (m, 2H), 7.5 (m, 3H), 7.64 (d, J=7Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_{11}$H$_{10}$F$_6$O$_2$, 288.0585; found, 288.0577.

1-bromo-4-methoxybenzene [8a]

^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 3.74 (s, 3H), 6.92 (d, J=8.7Hz, 2H), 7.46 (d, J=8.7 Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_7$H$_7$BrO, 185.9680; found, 185.9676.

1-bromo-4-ethoxybenzene [8b]

^{1}H NMR (300 MHz, DMSO-d$_6$) 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]$^+$ calcd for C$_8$H$_9$BrO, 199.9837; found, 199.9839.

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

^{1}H NMR (300 MHz, DMSO-d$_6$) 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=8.7 Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_{13}$H$_{19}$BrO, 270.0619; found, 270.0621.

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

^{1}H NMR (300 MHz, DMSO-d6) δ: 3.69 (m, J=4.5 Hz, 2H), 3.98 (t, J=4.5 Hz, 2H), 4.87 (brs, 1H), 6.90 (d, J= 8.7 Hz, 2H), 7.45 (d, J=8.7 Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_8$H$_9$BrO$_2$, 215.9786; found, 215.9779.

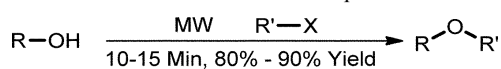### 2-(2-(4-bromophenoxy)ethoxy)ethanol [Byproduct-Entry 8d]

^{1}H NMR, (300 MHz, DMSO-d$_6$) δ: 3.49 (m, 4H), 3.74 (m, 2H), 4.0 (m, 2H), 4.61(brs, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.43 (d, J=8.7 Hz, 2H). HRMS (*m/z*): [M]$^+$ calcd for C$_{10}$H$_{13}$BrO$_3$, 260.0048; found, 260.0053.
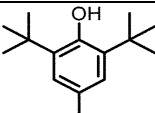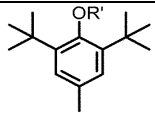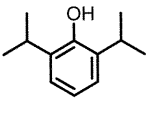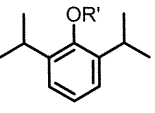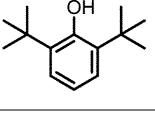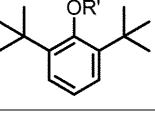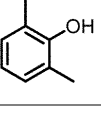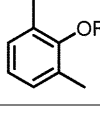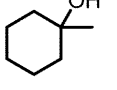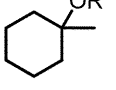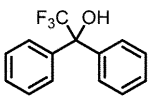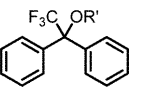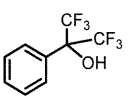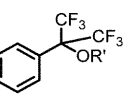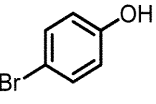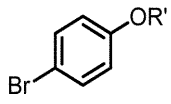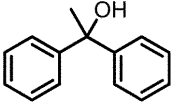
RESULT AND DISCUSSION

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.

Synthesis of (2,2,2-trifluoro-1-(heptyloxy)ethane-1,1-diyl)dibenzene from 2,2,2-trifluoro-1,1-diphenylethanol and 1-bromoheptane (**Entry 6c**) took least reaction time (8 min) at 80 ºC whereas reaction of 1,1-diphenylethanol with 1-bromoheptane (**Entry 9c**) took longer reaction time (15 min) at 100 ºC to get only 10% of desired product. In case of 2,2,2-trifluoro-1,1-diphenylethanol, the trifluoromethyl (CF_3) at 2-position makes the hydroxyl group more acidic compared to 1,1-diphenylethanol. Same result was observed for 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol (**Entry 7c**) where the reaction was completed within 8 minutes at 80 ºC.

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

$$R-OH \xrightarrow[\text{10-15 Min, 80\% - 90\% Yield}]{\text{MW} \quad R'-X} R-O-R'$$

Entry	R–OH	R–OR'	Time (min) / Temp (ºC)	Yield (%)
1			a. 10 / 100 ºC b. 10 / 100 ºC c. 10 / 100 ºC d. 12 / 100 ºC	a. 80 b. 82 c. 85 d. 80
2			a. 10 / 100 ºC b. 10 / 100 ºC c. 10 / 100 ºC d. 10 / 100 ºC	a. 75 b. 80 c. 78 d. 76
3			a. 10 / 100 ºC b. 10 / 100 ºC c. 10 / 100 ºC d. 10 / 100 ºC	a. 80 b. 80 c. 85 d. 80
4			a. 10 / 80 ºC b. 10 / 80 ºC c. 10 / 80 ºC d. 10 / 80 ºC	a. 75 b. 78 c. 85 d. 80
5			a. 10 / 80 ºC b. 10 / 80 ºC c. 10 / 80 ºC d. 15 / 80 ºC	a. 72 b. 75 c. 80 d. 75
6			a. 08 / 80 ºC b. 08 / 80 ºC c. 08 / 80 ºC d. 10 / 80 ºC	a. 80 b. 80 c. 85 d. 75
7			a. 08 / 80 ºC b. 08 / 80 ºC c. 08 / 80 ºC d. 10 / 80 ºC	a. 80 b. 85 c. 88 d. 75
8			a. 08 / 80 ºC b. 08 / 80 ºC c. 05 / 80 ºC d. 10 / 80 ºC	a. 82 b. 85 c. 80 d. 68
9		No Required Product	a. 10 / 100ºC b. 10 / 100ºC c. 10 / 100ºC d. 10 / 100ºC	a. NA b. NA c. NA d. NA

(a) Where R'–X=CH_3–I. (b) Where R'–X=C_2H_5–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 (pK_a 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-bromoheptane, it took 15 minutes at 100 ºC (**Entry 1c**) whereas 4-bromo phenol took 5 mins at 80 ºC (**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 ºC 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 –CF_3 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-diyldibenzene 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-bromophenoxy)ethoxy)ethanol as a byproduct. But the –OH group of 4-bromo phenol is more acidic in nature compared to the –OH attached to chlroethyl (–CH_2CH_2Cl) 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.

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