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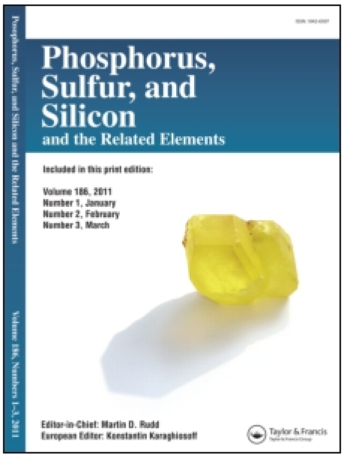

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A NEW PROTOCOL FOR O-METHYLATION OF PHENOLIC COMPOUNDS WITH TRIMETHYL PHOSPHITE OR TRIMETHYL PHOSPHATE UNDER SOLVENT-FREE CONDITION AND MICROWAVE IRRADIATION

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A simple method for the preparation of industrially important alkyl aryl ethers is reported. Several phenolic compounds such as phenols, naphthols, and hydroxy coumarins were O-methylated with trimethyl phosphite or trimethyl phosphate under microwave irradiation and solvent-free condition in almost quantitative yields. Reaction of 2-naphthol with trimethyl phosphate gave mixture of 2-methoxynaphthalene and 1-methyl-2-methoxynaphthalene while the reaction with trimethyl phosphite gave mostly 2-methoxynaphthalene. This method is highly efficient for the methylating of phenolic compounds with very easy experimental procedure and environmental friendly conditions.

Keywords: Alkyl aryl ethers; microwave irradiation; solvent-free; trimethyl phosphite

Alkyl aryl ethers are an industrially important class of compounds.[1] In particular, methyl aryl ethers have various usages in different chemical processes.[2] Methyl aryl ethers are useful as starting materials for the preparation of fragrances, dyes, and pesticides, as antioxidants in oils and fats or as stabilizers of plastics.[3]

There have been several approaches for the methylation of phenolic compounds. Dimethyl carbonate was used for O-methylation of phenols in the presence of potassium or cesium carbonate and phase transfer catalysts such as tertiary amines and pentaalkylguanidines at temperatures between 120 and 200°C under autogenous pressure for

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several hours.[4] Methyl aryl ethers, such as anisole, also were prepared from aryl bromides and concentrated sodium methoxide solutions in dimethyl formamide and methanol.[2] Alkyl methyl carbonates, methyl iodide, orthoesters, and dimethyl sulfate also were used to accomplish the O-methylation of phenolic compounds in the presence of alkaline base or potassium carbonate in polar solvents and in an autoclave or reflux conditions.[5] Gas solid phase transfer method was also reported for such a process using polyethyleneglycol (PEG) or crown ethers as phase transfer catalyst.[6]

Solvent-free media coupled with microwave promoted reactions are gaining more widespread use in organic chemistry. The published examples clearly show that microwave energy significantly reduces reaction time for a diverse selection of chemical processes traditionally performed under external heating.[7] In continuation of our work on solvent-free and microwave-assisted organic reactions,[8] we now report a very simple, fast, and general method for the O-methylation of phenolic compounds without using a solvent with trimethyl phosphit or trimethyl phosphate under microwave irradiation with almost quantitative yields.

Although trimethyl phosphite has been used in the conversion of carboxylic acids to the corresponding methyl ester under neutral condition, but to the best of our knowledge, there is not any report in the literature for using trimethyl phosphite as methylating agents for phenols and naphthols.

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RESULTS AND DISCUSSION

O-Methylation of phenolic compounds with other methylating agents can be carried out under conventional conditions after several hours, which is cumbersome and time consuming. By using trimethyl phosphite or trimethyl phosphate under microwave irradiation and solvent-free and environmentally benign conditions, the reaction time is significantly reduced from several hours to a few minutes, with improvement in the isolated yields. In addition trimethyl phosphite and specially trimethyl phosphate is a readily available and cheap reagent in comparison with other reported methylating agents. Thus when phenol and 1.1 equivalent of trimethyl phosphite or trimethyl phosphate were irradiated for about 1.0 min in a conventional microwave oven in the presence of 1.0 mL solution of BF_3 in ether, anisole was produced with more than 99% yield. The same reaction was performed for naphthols and several phenolic compounds. In all cases the corresponding methyl aryl ethers were produced with high yields (Scheme 1, Table I). In the

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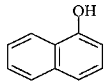
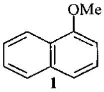
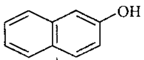
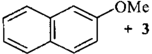
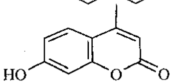
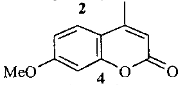
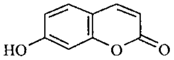
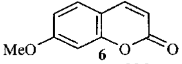
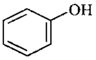
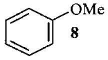
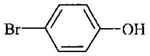
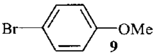
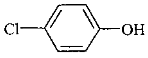
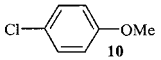
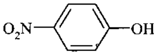
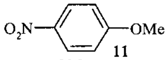
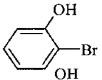
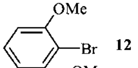
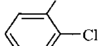
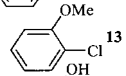
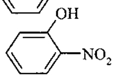
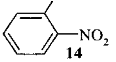
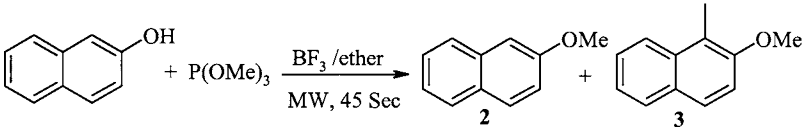
TABLE I Methylation of Phenolic Compounds with Trimethyl Phosphite

Entry	Substrate	Product	Time (s)	Yield (%)[a]
1		 1	65	85
2		 2	35	99[b]
3			40	92
4			55	93
5			90	88
6			120	86
7			180	85
8			180	84
9			150	74
10			150	76
11			180	72

[a] Isolated yields.

[b] Total yield for the mixture of 2-methoxynaphthalene and 1-methyl-2-methoxynaphthalene.

case of 2-naphthol, a mixture of 2-methoxynaphthalene and 1-methyl-2-methoxynaphthalene was produced with the ratio of 2 to 1 (Table I, entry 2).



SCHEME 1

When trimethyl phosphate was used for the methylation of 2-naphthol, 7-hydroxycoumarin and 4-methyl-7-hydroxycoumarin, a mixture of C- and O-methylating products was obtained. Since

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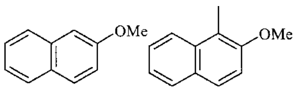
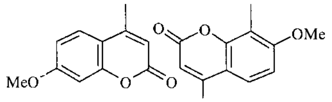
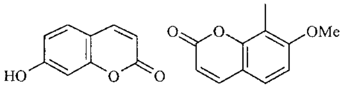
TABLE II C- and O-Methylation of Phenolic Compounds with Trimethyl Phosphate

Entry	Substrate	Product	Time (s)	Yield (%)[a]
1	2-naphthol	 2 (54 %) 3 (46 %)	45	99
2	4-methyl-7-hydroxy coumarin	 4 (64 %) 5 (36 %)	100	84
3	7-hydroxy coumarin	 6 (63 %) 7 (37 %)	90	81

[a]Isolated yields.

C-methylation of 2-naphthol is difficult and very time consuming,[9] this process can be used for the preparation of 1-methyl-2-methoxynaphthalene, 8-methyl-7-methoxycoumarin and 4,8-dimethyl-7-methoxycoumarin and two other phenolic compounds (Table II). By changing the irradiation time or microwave power, the ratio of C- to O-methylated products was not changed. Under these conditions 1-naphthol and other phenolic compounds gave only O-methylating products.

CONCLUSION

In conclusion, we report a mild and efficient method for the methylation of phenolic compounds by using trimethyl phosphite or trimethyl phosphate as the methylating agent under microwave irradiation and environmentally benign solvent-free condition with good to excellent yields.

EXPERIMENTAL

General

All yields refer to isolated products. The products were identified by comparison of their physical and spectral data (IR, NMR, and MS) with those obtained for known samples. The purity of the products was determined with TLC and GC. NMR spectra were recorded on a Bruker ACF

500. IR spectra were measured with the Perkin Elmer 1600 FTIR spectrometer. Mass spectra were obtained on Fisson 800 Trio, and GC-Mass HP 5973 MSD.

General Procedure for O-Methylation of Phenolic Compounds

A mixture of phenol (1.5 mmol), trimethyl phosphite or trimethyl phosphate (1.6 mmol), and BF_3/ether (1.0 mL) were placed in a closed glass container and subjected to microwave irradiation in a conventional oven with high power for 30 s to 3 min. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with a 5% solution of sodium hydroxide (2 × 20 ml) and then with water (2 × 20 ml), dried over $MgSO_4$, and evaporated to get the pure products.

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APPENDIX 1

Selected spectroscopic data: 2-Methoxy naphthalene, **1**, Solid, m.p., 69–72°C (lit., m.p. 70–73°C);[10a] ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.98 (s, 3H), 7.30–7.32 (m, 1H), 7.39–7.41 (m, 1H), 7.53–7.56 (m, 1H), 7.64–7.67 (m, 1H), 7.90–7.98 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 55.7 (CH_3), 106.4 (CH), 119.4 (CH), 124.1 (CH), 126.9 (CH), 127.8 (CH), 128.4 (CH), 129.6 (C), 130.1 (CH), 135.3 (C), 158.3 (C). IR (KBr), ν 3059.5, 3030.7, 3000.0, 2953.2, 1600.3, 1498.6, 1247.6, 1040.4, 784.6, 690.1 cm^{-1}.

7-Methoxy 4-methyl coumarin, **4**, Solid, m.p. 159–161°C (lit. m.p. 161–162°C),[10b] ^{1}H NMR (500 MHz, $CDCl_3$), δ 2.36 (s, 3H), 3.87 (s, 3H), 6.11 (s, 1H), 6.78 (d, $J = 2.3$ Hz), 6.84 (m, 1H) , 7.47 (d, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$), δ 19.0 (CH_3), 56.0 (CH_3), 96.5 (CH), 101.2 (CH), 112.4 (C), 113.9 (CH), 152.6 (C), 155.7 (C), 161.3 (C), 163.0 (C); MS, 190 (M^+), 162, 147 (base peak), 91, 77; IR (KBr), ν, 3356.6, 3097.2, 2961.2, 1730.5, 1523.1, 1445.3, 1392.3, 1261.3, 1051.5 cm^{-1}.

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