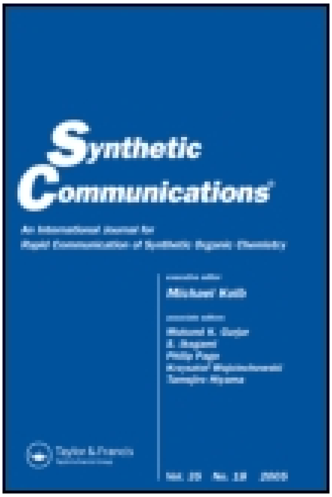

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Microwave-Assisted Protection of Phenols as tert-Butyldimethylsilyl (TBDMS) Ethers Under Solvent-Free Conditions

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Microwave-Assisted Protection of Phenols as *tert*-Butyldimethylsilyl (TBDMS) Ethers Under Solvent-Free Conditions

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Abstract: A facile, time-saving procedure to protect phenols with *tert*-butyldimethylsilyl chloride using imidazole as catalyst under solvent-free conditions is described. Several phenolic compounds with different substitution patterns can be silylated in high yield with substantially reduced generation of residues, a present goal in organic synthesis.

Keywords: Green chemistry, microwave, phenol protection, silyl ethers

INTRODUCTION

The temporary masking of phenols by a number of silylating agents plays a fundamental role in modern organic synthesis, polymer development, and synthetic biochemistry.[1] Since its discovery by Corey and Venkateswarlu,[2] the *tert*-butyldimethylsilyl (TBDMS) group is one of the most widely used protecting groups because of its stability in a variety of organic reactions and facility by which it can be introduced and removed under mild conditions. Usually, the reaction between *tert*-butyldimethylsilyl chloride (TBDMSCl) and the phenolic compound is performed in the presence of imidazole or 4-dimethylaminopyridine (DMAP) as catalyst and results in high yields of TBDMS ether formation.[2,3] However, the procedure for *tert*-butyldimethylsilylation of phenols is time consuming and involves the use of organic solvents such as DMF or THF.[4]

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In recent developments, the use of microwave irradiation (μW) has become a very popular tool to simplify and improve organic reactions, because the desired product is often obtained in high yield and shorter reaction times. Furthermore, the reactions might be performed under solvent-free conditions and therefore be considered green chemistry.[5] Khalafi-Nezhad et al. described a method for silylation of alcohols and phenols using triisopropylsilyl chloride (TIPSCl) and imidazole under microwave irradiation.[6] Hexamethyldisiazane (HMDS) was also used as silylanting agent in microwave-assisted protection of phenols.[7,8] Nevertheless, the ease of deprotection of the TBDMS group with several substances under mild conditions, including tetrabutylammonium fluoride (TBAF),[2] KF,[9] KOH/EtOH,[10] LiCl,[11] $ZrCl_4$,[12] and Cs_2CO_3,[13] among others,[1] is an advantage in the preparation of several organic compounds, especially in the synthesis of natural products.[14] Recently, a method of *tert*-butyldimethylsilylation of phenols using microwave dielectric heating and iodine as catalyst has been reported. However, high microwave power, large TBDMSCl excess, and workup with organic solvents are required.[15]

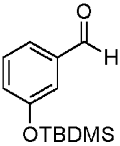
In this article, we report the conversion in high yield of several phenolic compounds to their corresponding TBDMS ethers using microwave-assisted synthesis in solvent-free conditions. Several variables were studied to determine optimal experimental conditions: (i) microwave power output, (ii) the time of irradiation, (iii) the amount of silylating agent, and (iv) the amount of catalyst required to obtain high yields of conversion.

RESULTS AND DISCUSSION

The reaction involves the dielectric heating of a mixture of TBDMSCl, the phenolic compound and imidazole, in absence of solvent. After 1 min of irradiation, with any microwave power, the reaction mixture (initially as a mixture of solids) melts in two phases. The yields obtained on protection of 3-hydroxybenzaldehyde as TBDMS ether after 1 min of irradiation varied slightly at the microwave power range between 180 W and 270 W. When power values higher than 270 W are used, lower yields are obtained (Table 1).

Several conditions were tested to assess the efficiency of the reaction (Table 2). Optimum experimental conditions were obtained using a small excess of TBDMSCl (1.2 eq.) and 2 eq. of imidazole. The use of a large excess of imidazole results in the complete conversion to the silylated product. However, direct distillation of the product is difficult under this condition, demanding an aqueous workup before purification. Large excess of the silylating agent should also be avoided as it results in a white fume from the reaction flask, with no significant increase in the yield. This fume is also observed if TBDMSCl is irradiated alone, which indicates that it originates from the silylating agent decomposition.

Table 1. Effect of microwave power on reaction yields of 3-hydroxybenzaldehyde with TBDMSCl (1.2 eq) and imidazole (2 eq.) after 1 min of irradiation

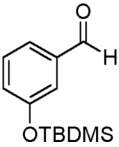
Product	Power (W)	Yield (%)[a]
	90	36
	180	74
	270	81
	360	74
	450	61

[a] GC yields

The dependence of the irradiation time on the formation of 3-(*tert*-butyldimethylsilanyloxy)benzaldehyde was also investigated. As depicted in Figure 1, the higher efficiency is obtained with an irradiation time of 3 to 6 min. Longer reaction times lead to a darkening of the reaction mixture and slightly lower yields of the silyl ethers are obtained.

We have examined the method's consistency with a variety of phenolic substrates with different substitution patterns (Table 3). In all cases, silyl ethers were obtained in good to excellent yields using low irradiation power (90 W) for 2 min and, after a cooling period, 2 min more at 180 W. The use of two heating cycles results in better yields than continuous irradiation at 90 or 180 W for 4 min. Products were identified by ^{1}H-NMR and ^{13}C-NMR spectra and comparison with previously reported spectroscopic data.[4,6] Purity was measured by gas chromatography of the distillated products. The

Table 2. Effect of reactant concentration on protection of 3-hydroxybenzaldehyde as TBDMS ether[a]

Product	TBDMSCl[b]	Imidazole[b]	Yield (%)
	1.0	1.0	71[c]
	1.2	1.0	81[c]
	2.0	1.0	88[c]
	1.0	2.0	87[c]
	1.2	2.0	97[c]
	1.5	2.0	98[c]
	2.0	2.0	97[c]
	1.0	3.0	90[d]
	1.5	3.0	99[d]

[a] For experimental conditions, see representative procedure.
[b] In equivalents.
[c] GC yield after direct distillation.
[d] GC yield after aqueous workup, extraction, and distillation.

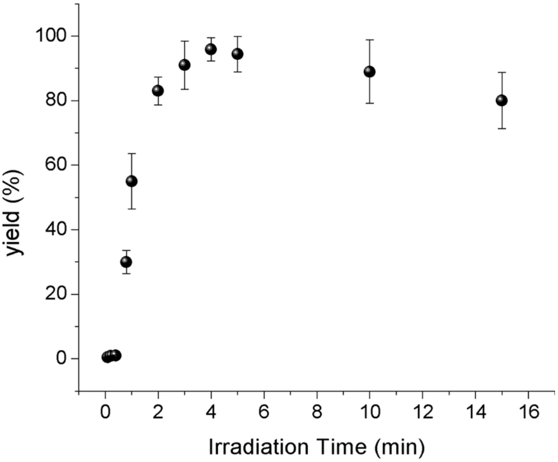


Figure 1. Dependence of 3-(*tert*-butyldimethylsilanyloxy)benzaldehyde formation on the irradiation time at 180 W, using TBDMSCl (1.2 eq.) and imidazole (2.0 eq.). The yields represent isolated silylated product after direct distillation. The error bars indicate mean values ± sd of at least three experiments.

utility of the method was also confirmed by the monosilylation of catechol and the protection, as TBDMS silyl ether, of resorufin (entry 10), a widely used fluorescent indicator.[16]

In summary, we have developed a mild and efficient method for the protection of phenolic compounds as TBDMS ethers. This method does not require long reaction times as the dielectric heating provided by microwave irradiation is used to accelerate the process. Moreover, the reaction is performed under solvent-free conditions and does not require aqueous workup. Silyl ethers are obtained in good to excellent yields upon low-power irradiation (90 W) for 2 min, a cooling period, and then followed by 2 min irradiation at 180 W, using small excess of TBDMSCl (1.2 eq.) and 2 eq. of imidazole. Thus, the use of this protocol for the preparation of TBDMS ethers substantially reduces the generation of residues, which is a present goal in organic synthesis.

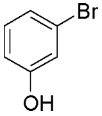
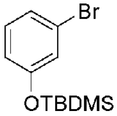
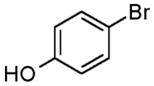
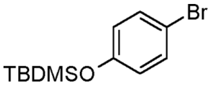
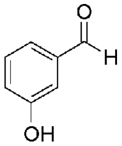
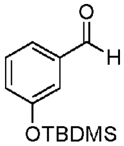
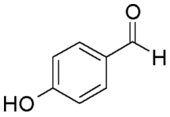
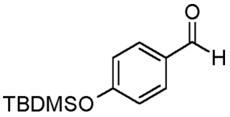
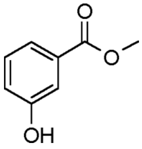
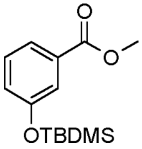
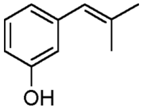
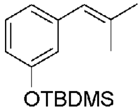
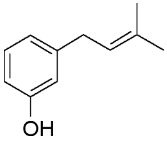
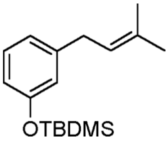
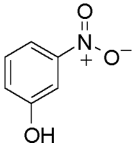
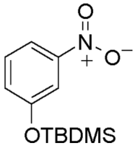
EXPERIMENTAL

General

All reactants were purchased at highest commercial quality and used without any further purification. 3-(2-Methylpropenyl)phenol and 3-(3-methyl-2-butenyl)phenol were prepared as described elsewhere.[4] Product formation was followed on a Shimadzu CG14A gas chromatograph

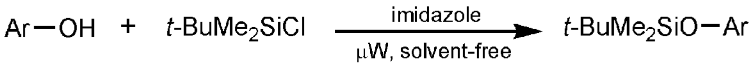
Table 3. Microwave-assisted protection of phenols with TBDMSCl/imidazole under solvent-free conditions[a]

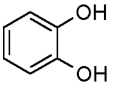
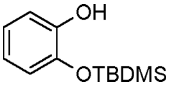
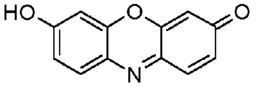
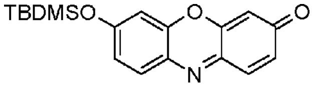
$$\text{Ar—OH} + t\text{-BuMe}_2\text{SiCl} \xrightarrow[\mu\text{W, solvent-free}]{\text{imidazole}} t\text{-BuMe}_2\text{SiO—Ar}$$

Entry	Substrate	Product	Yield (%)[b]
1			89
2			86
3			97
4			93
5			91
6			88
7			84
8			92

(*continued*)

Table 3. Continued



Entry	Substrate	Product	Yield (%)[b]
9			76
10			79

[a] For experimental conditions, see representative procedure.
[b] GC yield after direct distillation.

coupling with a flame ionization detector (FID), using a capillary column (Supelco SBP-1701, fused silica 30 m × 0.25 mm × 0.25 μm film thickness). The purification of the products was carried out using a bulb-to-bulb distillatory Kugelrohr apparatus (Büchi glass oven B-580). The ^{1}H and ^{13}C spectra were obtained in $CDCl_3$ using tetramethylsilane (TMS) as internal reference on a Bruker AC-200F and the mass spectra on a CG-MS Hewlett-Packard 5890/5988.

Representative Procedure

In a round-bottom flask, up to 15 g of phenolic compound, *tert*-butyldimethylsilyl chloride (1.2 eq.), and imidazole (2 eq.) are combined. This flask is put into a beaker, surrounded by vermiculite, and placed inside of a Samsung (MW6730 W, 900 W) microwave oven at 10 cm from the internal plate border. The reaction mixture is then heated for 2 min on a power setting of 10% (~90 W). Once the heating cycle is complete, two phases are formed inside the flask. After a cooling period, the reaction mixture is heated again on a power setting of 20% (~180 W) until the reactant is completely consumed, as determined by TLC. The products are purified by bulb-to-bulb distillation under reduced pressure using a Kugelrohr (Büchi glass oven B-580) apparatus. If an aqueous workup is required, the reaction mixture is poured into water and extracted with Et_2O. The combined organic phases are dried over anhydrous $MgSO_4$ and the solvent is evaporated under reduced pressure. The crude products are purified by distillation with a Kugelrohr (Büchi glass oven B-580) apparatus under reduced pressure. All microwave irradiations are carried out in an open system.

Characterization Data

(3-Bromophenoxy)*tert*-butyldimethylsilane (1). Bp (2 mmHg): 119–128°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.92. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.61–7.34 (m, 4H), 1.52 (s, 9H), 1.01 (s, 6H). MS m/z: 286 (M^+). Anal. calcd. for $C_{12}H_{19}BrOSi$: C, 50.17; H, 6.67. Found: C, 50.56; H, 6.81.

(4-Bromophenoxy)*tert*-butyldimethylsilane (2). Bp (3 mmHg): 119–125°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.90. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.35 (d, $J = 8.56$ Hz, 2H), 6.75 (d, $J = 8.56$ Hz, 2H), 1.37 (s, 9H), 1.07 (s, 6H). MS m/z: 286 (M^+). Anal. calcd. for $C_{12}H_{19}BrOSi$: C, 50.17; H, 6.67. Found: C, 50.54; H, 6.78.

3-(*tert*-Butyldimethylsilanyloxy)benzaldehyde (3). Bp (2 mmHg): 28–135°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.95. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.99 (s, 1H), 7.65–6.99 (m, 4H), 0.90 (s, 9H), 0.12 (s, 6H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 192.17, 158.02, 137.87, 130.07, 126.56, 123.55, 119.85, 25.58, 18.16, −4.46. MS m/z: 236 (M^+). Anal. calcd. for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53. Found: C, 66.19; H, 8.61.

4-(*tert*-Butyldimethylsilanyloxy)benzaldehyde (4). Bp (2 mmHg): 120–130°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.89. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 7.75 (d, $J = 8.79$ Hz, 2H), 6.91 (d, $J = 8.79$, 2H), 0.98 (s, 9H), 0.23 (s, 6H). MS m/z: 236 (M^+). Anal. calcd. for $C_{13}H_{20}O_2Si$: C, 66.05; H, 8.53. Found: C, 66.09; H, 8.55.

3-(*tert*-Butyldimethylsilanyloxy)benzoic acid methyl ester (5). Bp (2 mmHg): 125–128°C. R_f (SiO2, hexane/ethyl acetate; 5/2): 0.88. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.64–6.99 (m, 4H), 3.89 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H). MS m/z: 266 (M^+). Anal. calcd. for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.21; H, 8.40.

***tert*-Butyldimethyl[3-(2-methyl-propenyl)phenoxy]silane (6)**. Bp (3 mmHg): 132–138°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.85. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.90 (m, 4H), 6.17 (s, 1H), 1.82 (s, 3H), 1.79 (s, 3H), 0.94 (s, 9H), 0.21 (s, 6H). MS m/z: 262 (M^+). Anal. calcd. for $C_{16}H_{26}OSi$: C, 73.22; H, 9.98. Found: C, 73.44; H, 10.09.

***tert*-Butyldimethyl[3-(3-methyl-but-2-enyl)phenoxy]silane (7)**. Bp (0.5 mmHg): 100–110°C. R_f (SiO_2, hexane/ethyl acetate; 1/1): 0.68. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.96–6.43 (m, 4H), 5.13–5.12 (m, 1H), 3.09 (d, $J = 7.5$ Hz, 2H), 1.56 (s, 3H), 1.52 (s, 3H), 0.82 (s, 9H), 0.06 (s, 6H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 155.6, 143.3, 132.4, 129.1, 123.1, 121.3, 120.1, 117.2, 34.2, 25.8, 25.7, 18.2, 17.9, −4.4. MS m/z: 276 (M^+). Anal. calcd. for $C_{17}H_{28}OSi$: C, 73.85; H, 10.21. Found: C, 74.03; H, 10.29.

***tert*-Butyldimethyl(3-nitrophenoxy)silane (8)**. Bp (2 mmHg): 110–120°C. R_f (SiO_2, hexane/ethyl acetate; 5/1): 0.68. ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 156.20, 149.22, 130.37, 122.12, 115.99, 110.67, 25.82, 25.73, 18.21, 17.99, −4.47. MS m/z: 253 (M^+). Anal. calcd. for $C_{12}H_{19}NO_3Si$: C, 56.88; H, 7.56; N, 5.53. Found: C, 56.91; H, 7.60; N, 5.59.

2-(*tert*-Butyldimethylsilanyloxy)phenol (9). Bp (2 mmHg): 119–128°C. R_f (SiO_2, hexane): 0.36. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.21–7.02 (m, 4H), 5.69 (bs, 1H), 1.03 (s, 9H), 0.26 (s, 6H). MS m/z: 224 (M^+). Anal. calcd. for $C_{12}H_{20}O_2Si$: C, 64.24; H, 8.98. Found: C, 64.39; H, 9.06.

7-(*tert*-Butyldimethylsilanyloxy)resorufin (10). Bp (2 mmHg): 135–145°C. R_f (SiO_2, methanol): 0.51. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.61 (s. 1H), 7.05 (m, 2H), 6.62 (bs, 3H), 0.90 (s, 9H), 0.07 (s, 6H). MS m/z: 327 (M^+). Anal. calcd. for $C_{18}H_{21}NO_3Si$: C, 66.02; H, 6.46; N, 4.28. Found: C, 66.29; H, 6.67; N, 4.35. 7-(*tert*-Butyldimethylsilanyloxy)resorufin exhibits no considerable fluorescence emission; however, the corresponding anion, formed by TBAF-mediated deprotection, shows strong fluorescence with a maximum of $\lambda_{em} = 593$ nm.[16]

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