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RESEARCH PAPER

Chemoselective and Catalytic Trimethylsilylation of Alcohols and Phenols by 1,1,1,3,3,3-Hexamethyldisilazane and Catalytic Amounts of $PhMe_3N^+Br_3^-$

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Abstract: An efficient procedure for the trimethylsilylation of alcohols and phenols is presented. The combination of 1,1,1,3,3,3-hexamethyldisilazane and a catalytic amount of phenyltrimethylammonium tribromide ($PhMe_3N^+Br_3^-$) was found to be effective for the trimethylsilylation of alcohols and phenols. The protection reaction is very simple and homogenously performed in dichloromethane at room temperature and mild conditions.

Key words: phenyltrimethylammonium tribromide; alcohol; phenol; protection; trimethylsilylation; hexamethyldisilazane.

Synthetic methodology, as the building block of organic synthesis, continuously seeks new reagents, better reaction conditions, and more efficient and selective methods [1]. When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, the other reactive sites should be temporarily blocked [2]. Silyl ethers are the most popular protecting groups for alcohols and phenols in synthetic organic chemistry and various types of silyl ethers have been reported [3–5]. Trimethylsilylation is routinely used to protect alcohols and phenols, especially in steroids, sugars and natural product synthesis [6]. The silylation of alcohols is an important process not only as a method to protect alcohols but also for the synthesis of functional organosilicon compounds [7]. Generally, silyl ethers can be synthesized by the reaction of alcohols and phenols with hexamethyldisilazane [8–13], hydrosilanes [14], disilanes [15], alkylsilanes [16], allylsilanes [17], and trimethylsilyl azide [18] in the presence of a suitable catalyst. However, some of these procedures are not adequate for the chemoselective protection of the hydroxyl group for several reasons such as low selectivity, long reaction time, low product yield, toxicity, delicate purification, and lack of reactivity or difficulty in removing by-products. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) as a cheap, stable, and commercially available reagent is one of the most widely used silylating agents for the trimethylsilylation of alcohols and phenols. Its handling does not require special precautions and the reaction workup is not time-consuming because the by-product of the reaction is ammonia, which is simple to remove from the reaction media. However, the low silylating power of HMDS is the main drawback for its application. Therefore, to activate this reagent an appropriate catalyst is required.

1 Experimental

All the chemicals were purchased from Fluka, Merck, or Aldrich chemical companies. The oxidation products were characterized by a comparison of their spectral (IR, ^1H NMR, or ^{13}C NMR) and physical data with authentic samples. Phenyltrimethylammonium tribromide ($PhMe_3N^+Br_3^-$) is a commercially available material and was purchased from Merck.

The trimethylsilylation of 2-hydroxy-1,2-diphenylethanone (**1j**) with HMDS catalyzed by $PhMe_3N^+Br_3^-$ as a typical procedure is outline below. To a mixture of **1j** (0.212 g, 1 mmol) and hexamethyldisilazane (0.323 g, 2 mmol) in CH_2Cl_2 (10 ml), $PhMe_3N^+Br_3^-$ (0.018 g, 0.05 mmol) was added and the mixture was stirred at room temperature for 91 min (reaction progress monitored by thin layer chromatography). The reac-

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tion was then quenched with water (10 ml), and the organic phase was dried over Na_2SO_4 (3 g) and filtered after 10 min. Evaporation of dichloromethane gave 1,2-diphenyl-2-(trimethylsilyloxy)ethanone (0.276 g, 97%) as a white crystalline solid; m.p. 119–122 ºC; ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.36–7.51 (m, 8H), 5.92 (s, 1H), 0.15 (s, 9H); IR (nujol, cm^{-1}): ν 1 687, 1 597, 1 578, 1 458, 1 377, 1 251, 1 109, 979, 888, 844, 698.

Trimethyl(phenethoxy)silane (**2d**). ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.29 (s, 5H), 3.85 (t, 2H), 2.90 (t, 2H), 0.14 (s, 9H); IR (KBr, cm^{-1}): ν 3 029, 2 956, 1 605, 1 497, 1 454, 1 251, 1 095, 929, 883, 841, 748, 698.

Trimethyl(cholesteroloxy)silane (**2k**). ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.34 (m, 1H), 3.49 (m, 1H), 0.67–2.17 (m, 43H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 141.4, 121.3, 72.4, 56.9, 56.4, 50.4, 42.8, 42.4, 39.9, 39.6, 37.5, 36.6, 36.3, 35.9, 32.0, 28.3, 28.0, 24.4, 24.0, 22.8, 22.6, 21.2, 19.4, 18.8, 11.9, 0.36; IR (nujol, cm^{-1}): ν 2 853, 1 464, 1 456, 1 378, 1 249, 1 085, 896, 840.

Trimethyl(2-admantanoxy)silane (**2l**). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.78 (m, 1H), 1.35–2.25 (m, 14H), 0.08 (s, 9H); IR (nujol, cm^{-1}): ν 2 853, 1 450, 1 354, 1 249, 1 133, 1 093, 880, 839, 752.

Trimethyl(4-chlorophenoxy)silane (**2o**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.76–7.20 (dd, 71.5, 8.5, Hz, 4H), 0.02 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.7, 129.5, 122.8, 117.3, 2.3.

Trimethyl(2-methoxy-4-methylphenoxy)silane (**2r**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.70–6.84 (m, 3H), 3.87 (s, 3H), 2.36 (s, 3H), 0.34 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.6, 142.2, 131.4, 121.1, 120.6, 113.1, 55.5, 21.1, 0.6.

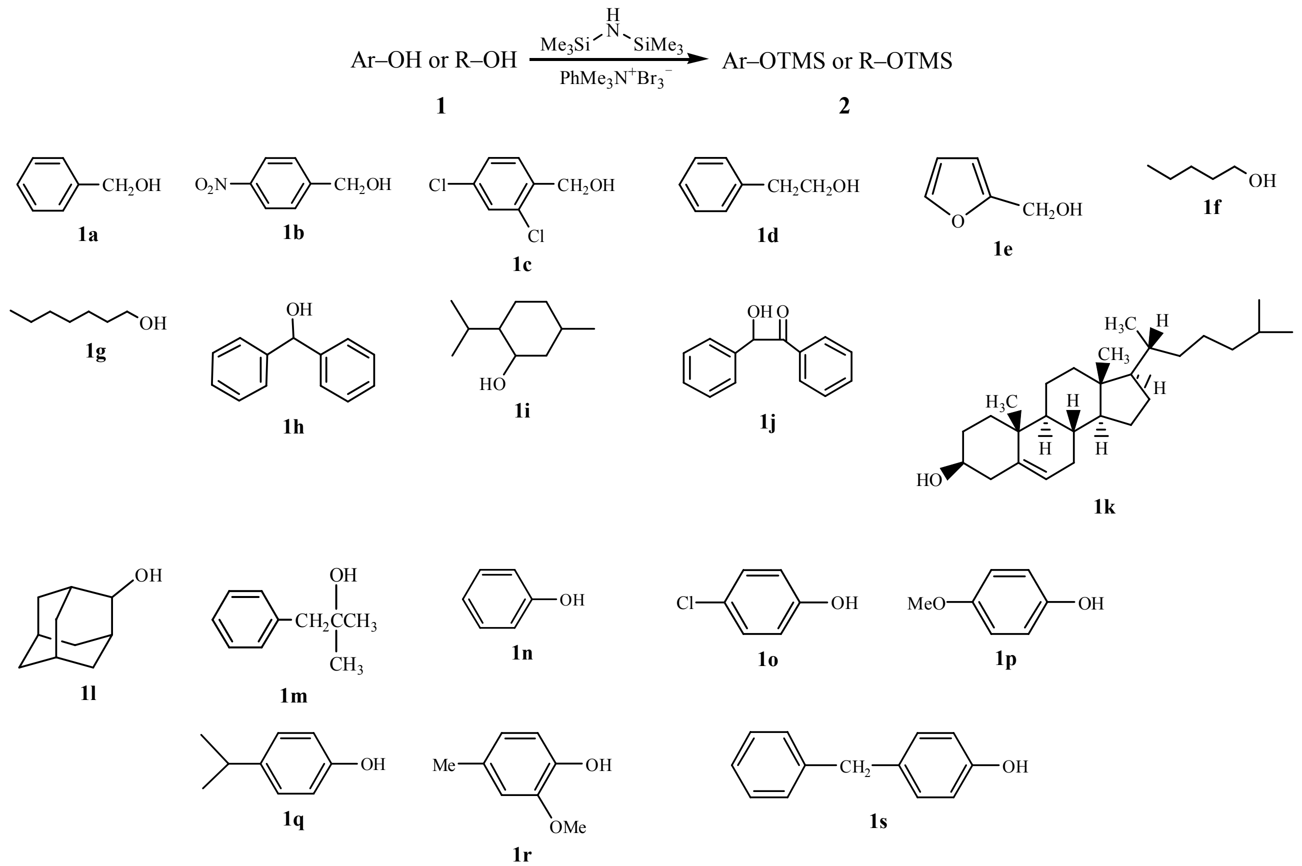
Trimethyl(4-benzylphenoxy)silane (**2s**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95–7.59 (m, 9H), 4.18 (s, 2H), 0.57 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.7, 141.7, 134.3, 130.2, 129.1, 128.8, 126.3, 120.2, 41.3, 0.53.

2 Results and discussion

As a continuation of our previous studies on the application of new reagents and catalysts in organic functional group transformations [19–26], we now disclose a new, efficient, and mild procedure for the trimethylsilyl protection of a wide range of alcohols and phenols using HMDS in the presence of catalytic amounts of $PhMe_3N^+Br_3^-$ under mild and homogenous conditions at room temperature.

Therefore, in this article, we report the efficient trimethylsilylation of different types of hydroxyl groups including primary, secondary, hindered secondary, and substituted phenols using HMDS (**I**) in the presence of a catalytic amount of $PhMe_3N^+Br_3^-$ (**II**) in dichloromethane at room temperature with good to excellent yields (Scheme 1 and Table 1).

As is evident from Table 1 a good range of turnover number (TON) and turnover frequency (TOF) for the catalyst is observed. To investigate the role of $PhMe_3N^+Br_3^-$ as the catalyst,



Scheme 1. Trimethylsilylation of different types of hydroxyl groups.