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Solvent-Free NaHSO₄-SiO₂-Catalyzed Efficient Tetrahydropyranylation of Alcohols and Phenols

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SOLVENT-FREE NaHSO₄-SiO₂-CATALYZED EFFICIENT TETRAHYDROPYRANYLATION OF ALCOHOLS AND PHENOLS

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GRAPHICAL ABSTRACT



Abstract A simple and efficient tetrahydropyranylation of alcohols and phenols has been developed using NaHSO₄-SiO₂ (0.5 mol%) as a catalyst under solvent-free conditions to yield corresponding tetrahydropyranyl ethers in excellent yields.

Keywords Silica-supported sodium hydrogen sulfate; tetrahydropyranylation; THP ether

INTRODUCTION

Tetrahydropyranyl (THP) is one of the most extensively employed protecting groups of alcohols in organic chemistry.^[1] Its ease of installation and cleavage, ready availability, and stability to a range of nonacidic reaction conditions such as hydrides, alkylating agents, Grignard reagents, and organometallic reagents makes THP ethers a good choice of protecting group. The THP group can be introduced by reacting an alcohol with dihydropyran (DHP) in the presence of a catalytic amount of an acid. Several acids including TsOH,^[2] pyridinium *p*-toluenesulfonate (PPTS),^[3] H₂SO₄-SiO₂,^[4] and Al(OTf)₃^[5,6] have been reported to affect tetrahydropyranylation of alcohols. However, most of the acid-catalyzed protocols reported so far suffer from long reaction times, high reaction temperatures, use of organic solvents, high catalyst loading, strong acidic conditions, and expensive and toxic acids.

Recently, Kamal et al. reported a solvent-free tetrahydropyranylation of alcohols using Al(OTf)₃ as a catalyst.^[6] Though this method is more efficient and

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Entry	Amount (mol%)	Temperature (°C)	Time (min)	Yield (%) ^a
1	0.5	0	60	77
2	1	0	30	82
3	0.5	25	5	90

 Table 1. Tetrahydropyranylation of benzyl alcohol at different temperatures and mol% catalyst loadings

^aIsolated yields.

environmentally friendly than the existing methodologies, taking aluminium triflate's high cost, moisture sensitivity, and need for workup using organic solvents into consideration, we felt there was scope for developing an alternative that is more efficient, is environmentally benign, and has relatively cheaper reaction conditions.

NaHSO₄ supported on silica gel has gained momentum as a viable and alternative acid catalyst for a number of transformations because of its low cost, ease of preparation, mildness, recoverability, reusability, and insensitivity to moisture. It has been applied as a catalyst in the opening of epoxides into β -hydroperoxy alcohols,^[7] synthesis of trisubstituted quinolines,^[8] β -enaminones,^[9] *N*-acylsulfonamides,^[10] aryl-14-*H*-dibenzo[*a.j*]xanthenes,^[11] amidoalkyl naphthols,^[12] coumarins,^[13] selective monoacetylation of unsymmetrical diols,^[14] and Ferrier rearrangement of glycals.^[15] Nishiguchi and coworkers reported monotetrahydropyranylation of symmetrical diols using NaHSO₄-SiO₂ and related metallic sulfates, M_m(SO₄)_n–SiO₂, as catalysts in a 1:1 DHP and hexane solvent system.^[16] Though NaHSO₄-SiO₂ has been listed as a catalyst in the study by Nishiguchi and coworkers, a thorough examination of the generality and scope of the catalyst for tetrahydropyranylation of alcohols and phenols under environmentally benign conditions has not been established yet.

In continuation of our work to develop new, environmentally benign, and cost-effective synthetic methodologies and in view of the efficiency of the NaHSO₄-SiO₂ as an acid catalyst, herein we report an efficient tetrahydropyranylation of alcohols and phenols using NaHSO₄-SiO₂ catalyst under solvent-free conditions in excellent yields.

RESULTS AND DISCUSSION

Tetrahydropyranylation of benzyl alcohol was used as a model reaction to investigate the optimal reaction conditions such as catalyst loading and temperature. The results are summarized in Table 1. In our first attempt, a solvent-free solution of benzyl alcohol and DHP was treated with 0.5 mol% of NaHSO₄-SiO₂ to afford the corresponding THP ether **2** in 77% yield in 1 h at 0 °C (Scheme 1). The rate of the



Scheme 1. Tetrahydropyranylation of benzyl alcohol.

Entry	Alcohol	Product	Time (min)	Yield (%) ^a
1	ОН	С ОТНР 2	5	90
2	Мео 3	MeO 4	5	95
3	OH	OTHP	10	84 (1:1)
4			10	94 (1:1)
5	и ОН 9	0 OTHP 10	5	65 ^b
6	ОН 11		5	85
7			5	80 ^c (mixture of diastereomers)
8			5	93 (1:1)
9	15 ————————————————————————————————————	16a and 16b OTHP 18	5	96
10	Br{	Br OTHP	5	94
11	МеООН 21	MeOOTHP 22	5	96
12	І—√ОН 23	иОТНР 24	5	91

Table 2. NaHSO₄-SiO₂-catalyzed tetrahydropyranylation of alcohols and phenols

(Continued)

Entry	Alcohol	Product	Time (min)	Yield (%) ^a
13	ОН	OTHP 26	30	92 ^{<i>c</i>}
14	OH 27	28 OTHP	5	95

Table 2. Continued

^aIsolated yields.

^bslightly low yields are as a result of the high volatility of the product.

^cTo dissolve the solid alcohols, 2.5 equivalence of DHP was used.

reaction was accelerated to 30 min by using 1 mol% of the catalyst without significant improvement in yield (82%) at 0 °C. However, when the reaction was carried out at room temperature using 0.5 mol% catalyst, it was completed in 5 min and provided 90% yield. Reducing the catalyst loading to 0.2 mol% resulted in a sluggish reaction and poor yields.

Variation in the total amount of DHP revealed that 1.5 equivalents were sufficient to fully convert the alcohol into the desired THP ether. Treatment of various primary and secondary alcohols in this way provided efficient access to the desired THP ethers. While tertiary alcohols were difficult to protect, the reactions proceeded remarkably well with the other alcohols as long as these were soluble in DHP. A slight excess, 2.5 equivalents, of DHP was required in the cases of furanose alcohol **13** (Table 2, entry 7) and the sterically hindered 2-iodophenol **25** (Table 2, entry 13). In all cases complete conversion of the starting alcohol was achieved in a short reaction time and products were identified by ¹H and ¹³C NMR spectroscopy after chromatographic purification. No aqueous workup was required as reaction mixtures were directly loaded onto silica gel for chromatographic purification.

The protocol compares very favorably with reported methods in terms of yield, catalyst loading, and reaction times. The reaction conditions are also tolerant of a range of acid-sensitive groups such allyl (Table 2, entry 5), propargyl (Table 2, entry 6), *p*-methoxy benzyl (Table 2, entry 2), trityl ethers (Table 2, entry 8), and acetals (Table 2, entry 7 and 8).

To evaluate the generality of the method, various phenols were treated under the optimized conditions to afford aromatic THP ethers. Interestingly, the reaction returned excellent yields of the THP ethers in short reaction times (Table 2, entries 9–14). Both activated and deactivated phenols reacted with DHP without significant discrepancy when compared with their corresponding aryl and aliphatic alcohols, showing the superiority of the method. In agreement with a recent report in which $Al(OTf)_3$ in dichloromethane^[7] was employed as a catalyst, the current method also resulted in tetrahydropyranylation of 2-naphthol in 95% yield, which otherwise has been found to be difficult to protect as a THP ether.

In conclusion, we have demonstrated that NaHSO₄ supported on silica gel under solvent-free conditions is an efficient catalyst for the tetrahydropyranylation of alcohols and phenols. The shorter reaction time, low catalyst loading, low cost and high stability of the catalyst, compatibility with a wide range of acid-sensitive groups, and absence of organic solvents (as solvents in both the reaction and workup) make the method attractive in organic synthesis, being greener and superior to the previously reported methods.

EXPERIMENTAL

Preparation of the NaHSO₄-SiO₂ Catalyst^[17]

Fourteen g of SiO₂ (column chromatographic grade, 60 Å, 200–400 mesh) was added to a solution of 5 g (0.04 mol) of NaHSO₄ in 25 mL of water in a 100-mL round-bottom flask. After stirring the mixture for 15 min at room temperature, the solvent was removed in vacuo at 40 °C until a free-flowing white solid was obtained. The catalyst was further dried in an oven maintained at 120 °C for 48 h prior to use.

General Procedure for the Tetrahydropyranylation of Alcohols and Phenols

To a mixture of alcohol (1.67 mmol) and dihydro-4*H*-pyran (2.5 mmol), NaHSO₄-SiO₂ (3 mg, 3 mmol NaHSO₄/g)^[17] was added. The reaction mixture was stirred at room temperature until thin-layer chromatographic (TLC) analysis showed complete disappearance of the starting material. After completion of the reaction, the mixture was directly loaded onto silica gel for chromatographic purification using 1:9 ethyl acetate–hexane eluent to afford corresponding THP ethers. The structures of the products were determined from their NMR spectra and by comparison with those reported in the literature (2,^[6] 4,^[6] 6,^[6] 8,^[6] 10,^[18] 12,^[6] 18,^[18,19] 20,^[6] 22,^[18] 24,^[20] 26,^[21] and 28.^[6]

(3a *R*,5 *R*,6 *R*,6a *R*)-2,2-Dimethyl-6-(tetrahydro-2*H*-pyran-2-yloxy)-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)tetrahydrofuro[2,3-*d*][1,3] dioxole (14)

Complex diastereoisomeric mixture was obtained; colorless oil; ¹H NMR (CDCl₃, 300 MHz): (5.99–5.82 (m, 1H), 4.79–4.10 (m, 5H), 4.01–3.33 (m, 6H), 1.86–0.81 (m, 18H); ¹³C NMR (CDCl₃, 75 MHz): δ 111.5, 105.1, 105.0, 104.9, 101.2, 101.1, 99.3, 99.2, 98.7, 98.4, 95.8, 95.6, 84.1, 84.0, 82.2, 81.5, 81.1, 79.7, 77.4, 77.0, 76.9, 76.6, 65.6, 65.1, 64.4, 64.3, 63.4, 63.3, 62.3, 62.2, 61.9, 61.6, 30.6, 30.5, 30.4, 26.8, 26.7, 26.2, 25.4, 25.3, 25.2, 19.8, 19.19.5, 19.3, 19.1, 19.0; HRMS (ESI) m/z (M + Na): calcd. 381.1889; found 381.1890.

(3a R, 5 R, 6 R, 6a R)-2,2-Dimethyl-6-(tetrahydro-2H-pyran-2-yloxy)-5-(trityloxymethyl)tetrahydrofuro[2,3-d][1,3]dioxole (16)

Diastereomeric mixture (1:1) was obtained; colorless oil; 16a:¹H NMR (CDCl₃, 300 MHz): δ 7.50–7.10 (m, 15H), 5.90 (d, J=3.9 Hz, 1H), 4.80–4.71 (m, 1H), 4.58–4.24 (m, 3H), 3.87–3.76 (m, 1H), 3.60–3.20 (m, 3H), 1.67–0.88 (m, 12H);

16b: ¹H NMR (CDCl₃, 300 MHz): $\delta 5.85$ (d, J = 3.6 Hz, 1H), 4.67 (d, J = 3.6 Hz, 1H), 3.14 (t, J = 8.7 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): $\delta 143.8$, 143.6, 128.7, 128.5, 127.8, 127.7, 127.0, 126.9, 111.6, 111.5, 104.9, 104.8, 100.6, 99.3, 94.5, 86.8, 86.7, 84.1, 82.0, 80.0, 79.5, 78.9, 76.4, 63.3, 61.8, 61.1, 60.1, 30.2, 30.0, 26.8, 26.2, 26.1, 25.15, 25.1, 19.7, 18.0; HRMS (ESI) m/z (M + Na): calcd. 539.2410; found 539.2405.

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