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SULFURIC ACID ADSORBED ON SILICA GEL. AN EFFICIENT CATALYST FOR THE TETRAHYDROPYRANYLATION OF ALCOHOLS

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Abstract: Sulfuric acid adsorbed on silica gel is an efficient catalyst for the tetrahydropyranylation of alcohols and phenols. The reaction takes 1 to 10 minutes to be completed and nearly quantitative yields are obtained. The method is remarkable simple and inexpensive.

The 2-tetrapyranyl (THP) group is one of the most versatile protecting groups for the alcohols and phenols in Organic Syntheses¹. Due to its stability under a variety of reaction conditions such as alkaline media, oxidant/reductant reagents, and alkylating/acylating reagents; THP ethers have extensively used for hydroxyl group protection.

We have found that sulfuric acid adsorbed on silica gel constitutes a useful catalyst to obtain, in a simple way, THP ethers (3) from alcohols and phenols (2). The



catalyst is easily prepared by mixing chromatographic grade silica gel (Merck Kiesegel 60, 70-230 mesh) with 3% of its weight of 98% sulfuric acid dissolved in acetone. After solvent removal, a yellow-brown powder is obtained, which can be stored in a desiccator for long periods of times without any appreciable loss of activity.

The procedure involves the treatment of a solution of an alcohol (2) in anhydrous dichloromethane with 2 equivalents of 3,4-dihydro-2H-pyran (1) in the presence of a catalytic amount of acidic silica gel; a complete conversion into the corresponding THP ether (3) is observed within 1 to 10 min (see table).

For relatively large scale reactions, the 3,4-dihydro-2H-pyran in dichloromethane is slowly added at low temperature (5-10°C) to the solution of the alcohol in the same solvent in the presence of acidic silica gel. A smooth reaction takes place resulting in the quantitative formation of the corresponding THP ether (3). Under these mild reaction conditions, even allylic and tertiary alcohols can be tetrahydropyranylated in nearly quantitative yields.

A number of methods²⁻⁹, mostly acid-catalyzed, for tetrahydropyranylation of alcohols involve excess of either 3,4-dihydro-2H-pyran, the catalyst, or both. In contrast to the reaction conditions and times of the other procedures, the present method utilizes very mild conditions and short reaction times. Most importantly, this method requires no aqueous work-up, which is substituted and reduced to a mere filtration and solvent evaporation. This feature furnishes a method especially useful for water sensitive compounds. The products are obtained in high yields and

| Entry | Substrate | Reaction Time (min) | Yield ^a (%) |
|-------|-----------|------------------------|---------------------------|
| | он | | |
| 2a | | 6 | 99 |
| 2b | | 5 | 93 |
| 2c | | 1 | 100 |
| 2d | С | 10 | 96 |
| 2e | но | 10 | 98 |
| 2f | Ом | 1 | 99 |
| 2g | OH OH | 3 | 94 |
| 2h | | 3 | 99 |
| 2i | | 10 | 93 |
| 2j | C D H | 1 | 95 |
| 2k | OH I | 5 | 98 |

Table. Tetrahydropyranylation of Alcohols and Phenols.

a) Yield of isolated product.

purities (95-99% by HPLC). If required, a final purification can be carried out by filtration through a silica gel column using hexane/ethyl acetate solvent mixtures. In short, this method provides a convenient procedure for tetrahydropyranylation of alcohols and phenols, which is remarkable simple and inexpensive.

Experimental Section

Adsorption of Sulfuric Acid on Silica Gel:

A solution of concentrated sulfuric acid (2 mL) in acetone (18 mL) is added to a suspension of silica gel (100 g, Merck Kiesegel 60, 70-230 mesh) in acetone (200 mL) at room temperature under vigorous stirring. After 1 h, the solvent is removed in a rotatory evaporator under reduced pressure (98 Torr) at 50°C for 4 h.

2-Tetrahydropyranylation of Alcohols and Phenols; General Procedure:

A solution of the alcohol (2a-K, 3.5 mmol) and freshly distilled 3,4-dihydro-2Hpyran (1, 7.0 mmol) in dichloromethane (13 mL) are stirred at room temperature in the presence of acidic silica gel (15 mg). After completion of the reaction, which usually takes 1-10 min, the catalyst is removed by filtration and 1-2 drops of triethylamine are added. The solvent is removed in a rotatory evaporator under reduced pressure and the residue is purified by column chromatography on silica gel using hexane/ethyl acetate as solvent to give the pure product (95-99% by HPLC).

Tetrahydropyranylation of 2-methyl-3-butyn-2-ol (2i); Large Scale Procedure:

To a solution of the alcohol 2i (200 g, 2.38 mol) in dry dichloromethane (1.4 L) at 0°C already containing acidic silica gel (1 g); is added slowly over a period of 15

min, under a nitrogen atmosphere, a solution of 3,4-dihydro-2H-pyran (3.5 mol) in dry dichloromethane (0.6 L). After completion of the addition, stirring is continued while the reaction is monitored by GLC (s.s. Column, 4.9 ft x 1/8 in, 10% OV-101 on chromosorb WHP 80-100 mesh, 180°C). Upon completion of the reaction, the catalyst is removed by filtration and a few drops of triethylamine are added. The solvent is removed in a rotatory evaporator to provide the crude product as an oil which is purified by fractional distillation (43-50°C at 10 Torr) to give 372 g of 3i.

¹H NMR Spectral Data of Compounds 3a-k.

- 3a: m.p. 100-101°C; NMR (CDCl₃) & 0.87(s,3H), 1.22(s,3H),
 0.92-2.54(m,25H), 3.26-4.06(m,3H), 4.60(bs,1H), 5.71 (t, 1H).
- **3b:** m.p. 152-153°C; NMR (CDCl₃) § 0.7-2.4(m,43H), 3.3-4.2 (m,3H), 4.7(bs,1H), 5.4(m, 1H).
- 3c: m.p. 137-138°C; NMR (CDCl₃) & 0.85(s, 3H), 1.08-2.55 (m, 19H),
 2.85(t,2H), 3.32-4.10(m,3H), 4.69(t,1H), 6.83-8.37(m,8H).
- 3d: Oil, column chromatography (hexane); NMR (CDCl₃) § 1.43-2.0(m, 6H), 3.43-4.0(m, 2H), 4.06-4.47(m, 2H), 4.69(t, 1H), 6.23-6.66(m, 2H), 7.2-7.43(m, 5H).
- 3e: m.p. 110.7°C; NMR (CDCl₃) & 0.7-2.0(m,34H), 3.3-4.0(m,6H), 4.6(s,2H).
- **3f:** b.p. 125-130°C(10 Torr); 97% HPLC; NMR (CDCl₃) § 1.3-2.2(m,6H), 3.4-4.1(m,6H), 4.7(t,1H), 6.8-7.4(m,5H).
- 3g: Oil, column chromatography (hexane/ethyl acetate); 97.7% HPLC;
 NMR (CDCl₃) δ 1.4-1.93(m,6H), 2.48(s,1H), 3.42-3.96(m,2H),
 4.13-4.28(m,2H), 4.74-4.9(m,1H), 5.08(t,1H), 6.87-7.40(m,5H)
- 3h: Oil, column chromatography (hexane/ethyl acetate); 99% HPLC; NMR (CDCl₃) & 0.2(s,9H), 1.3-1.9(m,6H), 3.3-5.1(m,6H), 6.8-7.4(m,5H).

- **3i:** b.p. 43-50°C (10 Torr); 99% HPLC, NMR (CDCl₃) ≤ 1.8-1.35(m,12H), 2.4(s,1H), 3.3-4.1(m,2H), 5.1(m,1H).
- 3j: Oil, column chromatography (hexane); NMR (CDCl₃) § 1.4-2.1(m, 6H),
 3.4-4.0(m,2H), 5.3(t,1H), 6.9-7.4(m,5H).
- **3k:** m.p. 38.5-39.6°C; NMR (CDCl₃) § 1.4-2.2(m,6H), 3.4-4.0(m,2H), 5.5(t,1H), 7.0-8.4(m,7H).

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