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SULFURIC ACID ADSORBED ON SILICA GEL. A MULTIPURPOSE ACID
CATALYST¹

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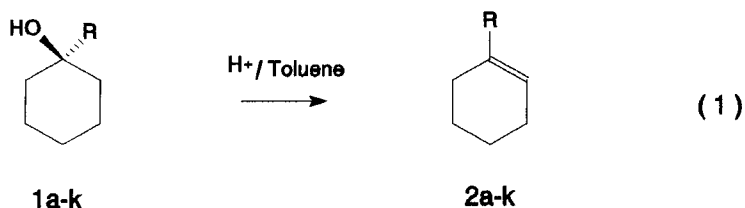
Abstract: A series of acid catalyzed reactions like the dehydration of alcohols, conversion of ketones to 1,3-dioxolanes and their hydrolysis, α,β -unsaturated ketones to enol ethers, and alcohols to methyl-methoxyethyl ethers are performed efficiently in high yield with sulfuric acid adsorbed on silica gel as catalyst.

The synthetic utility of supported reagents has been demonstrated during the past ten years^{2,3}. As a result, many reactions can be now carried out cleanly and rapidly under mild conditions by using reagents which have been

previously adsorbed on inorganic supports. Silica gel has been one of the most used inorganic supports in organic syntheses⁴⁻¹².

We wish to report the use of adsorbed sulfuric acid on silica gel as an efficient catalyst for a variety of acid catalyzed reactions such as dehydration of alcohols, preparation of α,β -unsaturated ketone enol ethers, preparation and hydrolysis of 1,3-dioxolanes, and protection of alcohols as 1-methyl-1-methoxyethyl ethers. This catalyst is easily prepared by mixing chromatographic grade silica gel (Merck Kieselgel 60, 70-230 mesh) with 3% of its weight of sulfuric acid dissolved in either methanol or acetone. After solvent removing at 45-50°C under vacuum (98 torr) for 4h, a dry yellow powder is obtained, which changes to dark brown color on time without any appreciable loss of activity.

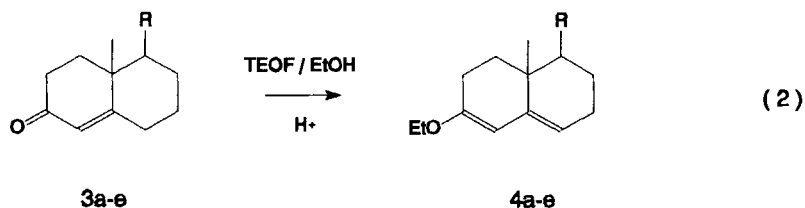
This powder is an efficient catalyst for the dehydration of secondary and tertiary alcohols (Eq.1).



R = H, alkyl

The dehydration is accomplished via a heterogeneous reaction between the alcohol and catalyst in toluene at 55-100°C (Table 1). Tertiary alcohols (substrates 1f-1i) are dehydrated faster than secondary ones and this suggest that a carbonium ion could be involved during the dehydration process. This assumption is supported by the observed regioselectivity (Saytzeff orientation), a fast epimerization process for some alcohols, and a conversion of epimeric alcohols into the same alkene. Furthermore, the stereochemistry for epimeric alcohols plays an important role in the dehydration rate, thus alcohols that exhibit a trans-diaxial orientation (substrates 1b, and 1k) are more susceptible to dehydration at lower temperatures and shorter reaction times.

The present catalyst manifests to be useful for some acid catalyzed carbonyl reactions. For instance, α,β -unsaturated ketosteroid enol-ethers are easily prepared within 1 to 2 h at room temperature (Eq.2).



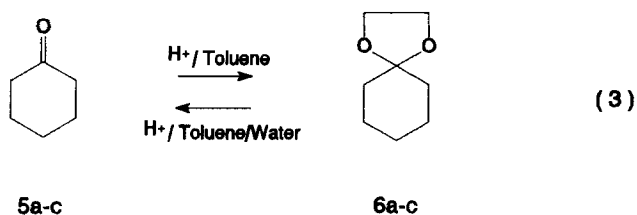
The reaction is performed by dissolving the steroid and two equivalents of triethyl orthoformate in either

Table 1. Dehydration of Alcohols with Sulfuric Acid Adsorbed on Silica Gel.

Entry	Substrate	Product	Time(H)/ Temperature°C	Yield (%)
1a			11 / 105	80
1b			1 / 100	83
1c			4 / 100	70
1d			2 / 100	77
1e			3 / 105	80
1f			1 / 45	83
1g			0.5 / 100	90
1h			0.5 / 100	95
1i			3 / 90	98
1j			6 / 105	93
1k			1 / 105	91

tetrahydrofuran or absolute ethanol in the presence of the catalyst (5-10% w/w). One of the advantages, among others, is its work up that involves a simple catalyst filtration, solvent removing, and crude product purification by crystallization. Representative examples are presented in Table 2. It is noteworthy that substrate 3c also gives appreciable amount of the corresponding 17-enol-ether. Nevertheless, a partial hydrolysis during the work up affords pure enol ether 4c.

The catalyst is also convenient for the ketalization of ketosteroids (Eq.3).



To carry out the reaction, the substrate, two equivalents of ethylene glycol, and the catalyst (10% w/w) in toluene are refluxed for 1 h and the by-product water is removed through a Dean-Stark trap. Pure products are obtained in good yield after a filtration through a small pad of silica gel (Table 3). The catalyst is efficient not only for preparation of 1,3-dioxolanes but also for their hydrolysis under mild conditions. As shown by the results in table 3,

Table 2. Conversion of α,β -unsaturated ketosteroids to enol-ethers by using sulfuric acid adsorbed on silica gel as catalyst.

Entry	Substrate	Product ^a	Time/H	Yield (%)
3a			1.5	99
3b			2.0	75
3c			2.0	89
3d			1.5	85

a. The reactions were performed on absolute ethanol except 3a which was carried out in a mixture of dioxane-dichloromethane.

Table 3. Conversion of ketosteroids to 1,3-dioxolanes and their hydrolysis to ketosteroids with sulfuric acid adsorbed on silica gel as catalyst.

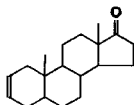
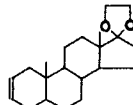
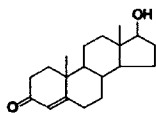
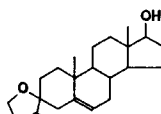
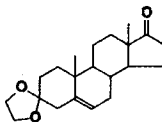
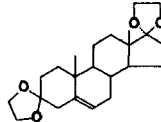
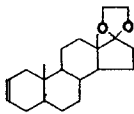
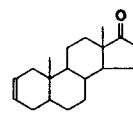
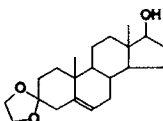
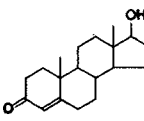
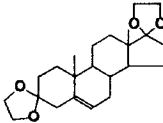
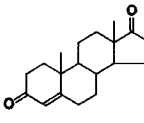
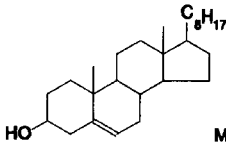
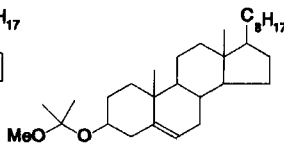
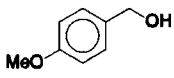
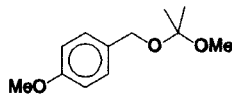
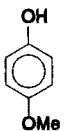
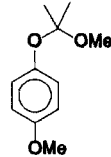
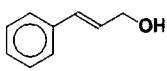
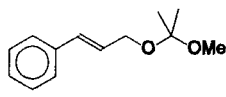
Entry	Substrate	Product	Time/H	Yield (%)
1,3-Dioxolanes				
5a			1.0	98
5b			1.0	83
5c			1.0	77
Hydrolysis				
6a		5a 	0.2	99
6b		5b 	0.5	98
6c		3c 	2.0	92

Table 4. Protection of alcohols as 1-methyl-1-methoxy ethyl ethers by using sulfuric acid adsorbed on silica gel as catalyst.

Entry	Substrate	Product	Time/min	Yield(%)
7a			5	84
7b			5	89
7c			5	97
7d			5	99

Experimental Section

Dehydration of Alcohols; General Procedure:

A solution of the alcohol (1a-k, 10 mmol) in toluene and the catalyst (30% w/w) are stirred under conditions given

in table 1. After completion of the reaction, the catalyst is removed by filtration and the solvent evaporated under reduced pressure. The residue is purified either by crystallization or via a chromatography column of silica gel using hexane/ethyl acetate as eluent solvent.

α,β -Unsaturated Keto Enol-Ethers; General Procedure:

A solution of the steroid (3a-d, 10 mmol) in absolute ethanol or tetrahydrofuran, freshly distilled triethyl orthoformate (20 mmol), and the catalyst (5-10% w/w) are stirred at room temperature (2-3 h). After completion of the reaction, the catalyst is removed by filtration and 2-3 drops of triethylamine are added. The solvent is evaporated in a rotatory evaporator under reduced pressure. Crude products are purified by crystallization from dioxane-water (4a), ethanol-heptane (4b), ethanol (4c), and 2-propanol (4d).

1,3-Dioxolane Ketosteroids; General Procedure:

A solution of the ketosteroid (5a-c, 20 mmol), ethylene glycol (40 mmol), and the catalyst (10% w/w) are heated at reflux temperature for 1-2 h. The water by-product is removed through a Dean-Stark trap. The reaction is monitored by TLC and when complete, the catalyst is removed by filtration. The solvent is evaporated under reduced pressure and the crude product purified by crystallization from toluene-ethanol (6a, 6c) or methanol (6b).

1,3-Dioxolane Hydrolysis; General Procedure:

A solution of the ketal (6a-c, 20 mmol) in wet toluene (2% water) and the catalyst (200% w/w) are stirred under the conditions given in table 4. After completion of the reaction, the catalyst is removed by filtration and the solvent evaporated. The crude product is purified by crystallization from methanol (8a), acetone-hexane (8b), and heptane (3c).

1-Methyl-1-methoxyethyl Ethers; General Procedure:

A solution of the alcohol (7a-d, 20 mmol) in anhydrous methylene chloride and 2-methoxypropene (40 mmol) is cooled at 5°C. The catalyst (0.5% w/w) is added and the reaction monitored by TLC which is usually complete between 3 to 5 min. Then, the catalyst is removed by filtration and the solvent evaporated. The crude product is purified through a small pad of silica gel which has been previously washed with hexane-triethylamine to avoid product hydrolysis.

Analytical Data of Compounds

- 2a-b:** m.p. 103-105°C. Reported¹⁴ 108-109°C; ¹H-NMR(CDCl₃)
δ 0.78(s,3H), 0.86(s,3H), 1.0-2.6(m,20H),
5.57(m,2H).
- 2c:** m.p. 135-138°C. Reported¹⁵ 139-142°C; ¹H-NMR(CDCl₃)
δ 0.67(s,3H), 0.93(s,3H), 2.12(s,3H), 1.02-
2.67(m,18H), 5.68(m,3H).
- 2d:** m.p. 79-80°C; Reported¹⁶ 80-81°C.
- 2e:** m.p. 148-150°C; Reported¹⁵ 149-150°C.

- 2f:** Oil; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 2.12(s,3H), 2.29(m,2H), 2.83(t,2H), 5.92(m,1H), 7.18-7.30(m,4H). MS m/z (relative intensity) 144(41), 129(100), 115(20), 102(5), 91(5), 77(7), 71(11). Anal. Calcd for $\text{C}_{11}\text{H}_{12}$: C,91.61; H,8.38. Found: C,91.57; H,8.44.
- 2g:** Oil; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 2.31-2.42(m,2H), 2.85(t,2H), 6.03-6.12(m,1H), 6.48-6.55(m,1H), 7.05-7.20(m,4H). MS m/z (relative intensity) 130(100), 115(12), 102(16), 98(2), 89(9), 77(21), 63(24). Anal. Calcd for $\text{C}_{10}\text{H}_{10}$: C,92.25; H,7.74. Found: C,92.10; H,7.89.
- 2h:** Oil; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 2.22-2.32(m,2H), 2.70(t,2H), 3.75(s,3H), 5.97-6.06(m,1H), 6.37-6.43(m,1H), 6.59-7.00(m,3H). MS m/z (relative intensity) 160(100), 145(46), 129(41), 115(75), 102(13), 91(28), 77(10), 63(20). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}$: C, 82.46; H,7.55; O,9.98. Found: C,82.67; H,7.97; O,9.35.
- 2i:** m.p. 102.6-103°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.63(s,3H), 1.86(s,3H), 2.02(s,3H), 3.89(s,3H), 7.0-7.8(m,6H). MS m/z (relative intensity) 226(100), 211(55), 196(25), 179(36), 165(41), 152(37), 139(21), 128(19), 115(29), 105(9), 98(6), 89(11). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}$: C,84.91; H,8.01; O,7.07. Found: C,83.65; H,8.34; O,8.00.
- 2j-k:** m.p. 66-69°C Reported¹⁷ 69-70 C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.67(s,3H), 0.78(s,3H), 0.83(s,3H), 0.89(s,3H), 0.93(s,3H), 0.5-2.4(m,29H), 5.29(s,2H).
- 3c:** m.p. 171-175°C; Reported¹⁸ 173-174°C.
- 4a:** m.p. 146.2-153.2°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.69(s,3H), 0.98(s,3H), 2.00(s,3H), 2.10(s,3H), 1.08-3.15(m,20H), 3.77(q,2H), 5.08(s,1H), 5.28-5.15(m,1H). MS m/z (relative intensity) 400(13), 340(3), 315(2), 297(4), 267(3), 251(3), 225(2), 201(4), 185(3), 164(5), 147(6), 133(13), 105(9), 91(14), 79(9). Anal. Calcd for $\text{C}_{25}\text{H}_{36}\text{O}_4$: C,74.96; H,9.05; O,15.97. Found: C,74.63; H,9.08; O,16.28.
- 4b:** m.p. 103.5-104.6°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.80(s,3H), 1.00(s,3H), 0.9-2.45(m,20H), 3.65(t,1H), 3.78(q,2H), 5.10(s,1H), 5.12-5.28(m,1H). MS m/z (relative intensity) 316(100), 301(18), 229(4), 203(6), 187(6), 173(12), 152(28), 145(19), 133(27), 121(38), 107(48), 91(81), 79(61). Anal. Calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2$: C,79.69; H,10.19; O,10.11. Found: C,79.24; H,10.23; O,10.52.

- 4c:** m.p. 149.5-151.4°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.91(s,3H), 1.00(s,3H), 0.8-2.7(m,20H), 3.78(q,2H), 5.11(s,1H), 5.15-5.20(m,1H). MS m/z(relative intensity) 314(100), 299(17), 286(7), 271(10), 216(8), 201(7), 187(11), 173(11), 164(24), 149(22), 129(21), 121(36), 105(46), 91(86), 79(66). Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{O}_2$: C,80.20; H,9.61; O,10.17. Found: C,79.88; H,9.57; O,10.54.
- 4d:** m.p. 141.6-142.4°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.92(s,3H), 1.31(t,3H), 1.10-2.63(m,18H), 3.70-3.87(m,2H), 5.22(s,1H), 5.29-5.38(m,2H). MS m/z(relative intensity) 300(100), 272(10), 257(6), 215(6), 176(14), 150(43), 122(50), 107(44), 91(85), 79(75). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_2$: C, 79.95; H,7.39; O,10.65. Found: C,78.82; H,7.29; O,11.88.
- 5a:** m.p. 103-105°C; Reported¹⁴ 108-110°C.
- 5b:** m.p. 153-157°C; Reported¹⁹ 155°C.
- 6a:** m.p. 117.6-122.2°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.79(s,3H), 0.90(s,3H), 0.8-2.3(m,20H), 3.87(s,4H), 5.6(s,2H).
- 6b:** m.p. 164.9-169.7°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.80(s,3H), 1.05(s,3H), 0.6-2.7(m,17H), 3.64(t,2H), 3.95(s,4H), 5.28-5.40(m,1H).
- 6c:** m.p. 171.3-171.4°C.
- 8a:** m.p. 117-119°C; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 0.69(s,3H), 0.70(s,3H), 0.91(s,3H), 1.00(s,3H), 1.35(s,6H), 3.10(s,3H), 0.6-2.4(m,32H), 5.2-5.35(m,1H). Anal. Calcd for $\text{C}_{31}\text{H}_{54}\text{O}_2$: C,81.16; H, 11.86; O,6.97. Found: C,81.03; H,11.63; O,5.80.
- 8b:** Oil, Hexane; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.42(s,6H), 3.43(s,3H), 3.76(s,3H), 6.77-7.01(m,4H). MS m/z(relative intensity) 210(1), 178(15), 163(1), 147(2), 137(8), 121(100), 109(6), 91(11), 77(24), 73(63), 65(5), 51(7), 43(19). Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C,68.54; H,8.62; O,22.82. Found: C,68.64; H,8.16; O,23.20.
- 8c:** Oil, Hexane; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.4(s,6H), 3.20(s,3H), 3.66(s,3H), 4.36(s,3H), 6.66-7.36(m,5H). MS m/z(relative intensity) 196(7), 181(5), 165(22), 137(7), 124(75), 109(22), 105(2), 92(6), 77(10), 73(100), 64(10), 52(10), 43(44). Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$: C,67.32; H,8.21; O,24.46. Found: C,68.13; H,8.57; O,23.30.

8d: Oil, Hexane; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.53(s,3H), 1.60(s,3H), 3.30(s,3H), 4.0-4.4 (m,2H), 6.1-6.8(m,2H), 7.0-7.6 (m,5H). MS m/z (relative intensity) 206(2), 191(1), 174(1), 159(1), 148(20), 133(7), 117(100), 105(12), 97(2), 91(25), 73(86), 65(6), 51(9), 43(30). Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C,75.69; H,8.79; O,15.51. Found: C,75.25; H,7.98; O,16.77.

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