

NOTE

KHSO₄-SiO₂-MeOH – An efficient selective solid-supported system for deprotection of alcohols from esters

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KHSO₄-SiO₂ can efficiently deprotect alcohols from esters through transesterification in methanol under mild condition. Esters of aromatic alcohols are easily transesterified at room temperature compared to the corresponding aliphatic or alicyclic alcohol. *N*-Acetyl compounds and ethers are resistant to the reagent under the above condition. The method is very useful for preparation of bio-diesel methyl ricinoleate from castor oil.

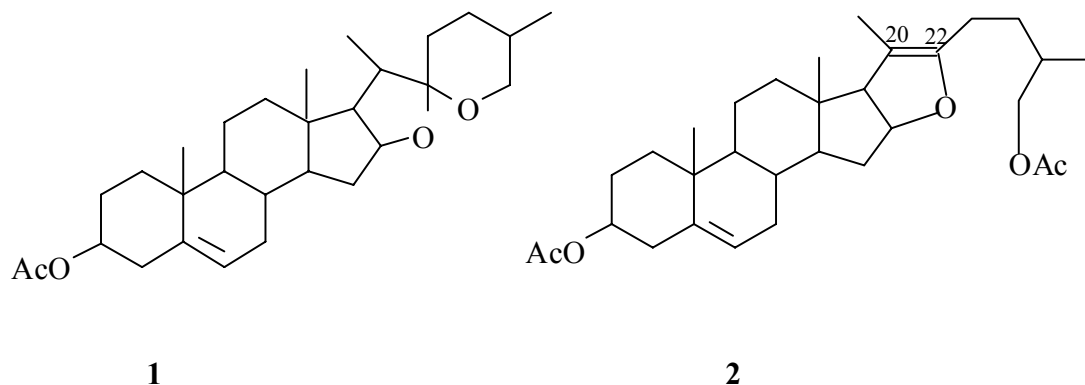
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Ester hydrolysis is an important fundamental reaction for deprotection of alcohols generally carried out either by chemical or biochemical methods. Chemical methods involve hydrolytic¹ or non-hydrolytic² methods using homogeneous or heterogeneous reagents. Because of the advantages of recycling and easy separability from the reaction mixture solid-supported heterogeneous catalysts³ are attractive from the economic and environmental point of view. Solid-supports such as alumina^{3b}, zeolite^{3c}, acid resin⁴, etc that are generally in use suffer from certain limitations such as requirement in large volume, pore size dependency, substrate specificity, etc.

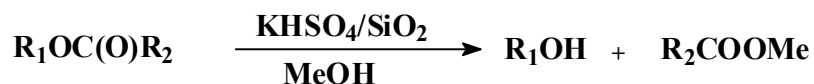
Recently selective cleavage of only prenyl esters using silica-supported sodium hydrogen sulphate in a nonprotic solvent was reported⁵. In this system groups other than the prenyl are resistant to deprotection. The deprotection was carried out in a non-protic solvent dichloromethane. In this system the proton required for the reaction is supplied by the prenyl part which subsequently releases 2-methyl-1,3-butadiene. But in a chance discovery we came across the KHSO₄-SiO₂-MeOH system where the alcohol system is not affected.

Results and Discussion

In continuation of the work on steroidal drug intermediates^{6a,b} efforts have been carried out to develop a non-acetic anhydride route⁷⁻⁹ to convert diosgenin acetate **1** to furostadiene derivative **2** using ethyl acetate¹⁰. The presence of spiro ethers in **1** is tempted to use mild acidic reagent KHSO₄ for this purpose that has found application in dehydration of alcohols¹¹, several acid catalyzed reactions^{12a,b,c} such as deprotection of TBDMS ethers, Diels–Alder reactions and preparation of *bis*-indolyl methanes, etc.



We carried out the reaction of diosgenin monoacetate **1** by refluxing in ethyl acetate in presence of KHSO₄ for 5 hr. The reaction did not proceed as expected. However, a mixture of ethyl acetate and methanol (1:1) produced deacetylated product diosgenin with 50% yield on refluxing for 20 hr. The conversion reduced to 30% when water was added (water EtOAc : MeOH, 1:1:1). From this it was clear that methanol, a protic solvent alone was responsible for the deprotection. In order to study the reaction a solid-supported KHSO₄ – SiO₂ was prepared to examine its activity against esters. It was observed that diosgenin acetate **1** was converted to its corresponding alcohol diosgenin on refluxing in methanol in presence of KHSO₄ – SiO₂ **Scheme I**.



Scheme I

yield. Similarly cholesteryl acetate was deacetylated in 8 hr (Entry **3**). The reaction did not proceed in ethyl acetate or acetonitrile alone. Castor oil can be very easily transformed into bio-diesel methyl

ricinoleate¹³. Presence of water (5%) inhibited the reaction. *N*-Acetyl compounds and ethers were resistant to the reagent. Aromatic esters were easily transesterified (Entry 7-9). The reagent could be recycled 4 times. The surface of silica gel probably formed a reaction field where reagents and substrates were accumulated by absorption and bound the reactants in close proximity for the reaction to occur⁷. In conclusion, a novel method has been developed for hydrolysis of esters using solid-supported heterogeneous catalyst.

Experimental Section

Chemicals:

All the chemicals were of AR grade and needed no further purification. Potassium hydrogen sulfate silica gel (6—120 mesh) and methanol were obtained from Merck India Ltd. All the alcohols used were from Sigma-Aldrich and Merck India Ltd.

Catalyst preparation

KHSO₄ (10 g, 72 mmole) was dissolved in 100 mL distilled water to have clear saturated solution. The solution was soaked completely in silica gel (25 g, 60-120 mesh). The soaked mixture was thoroughly mixed and dried in a hot oven at 150°C. for 24 hr to have free flowing powdery solid. The dried solid mixture was then kept in vacuum desiccator to use as stock solid support in different reactions.

General procedure for deprotection of alcohols

A solution of ester (0.21mmole) in methanol (10 mL) was added cautiously to KHSO₄-SiO₂ solid support (0.2 g) from the stock that contains 0.057 g(0.42 mmole) of KHSO₄ and 0.14 g (2.33 mmoles) of silica gel keeping the molar ratio of the substrate to KHSO₄ in 1:2. Stirred the entire mixture for about an hour and refluxed for 1-10 hr. Then the solvent was removed under reduced pressure. Water (10 mL) was added to the concentrated mass and the aqueous layer in ethyl acetate (3 x 20 mL) was extracted and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography to get pure alcohol. The alcohols and methyl esters

isolated were identified from their characteristic spectroscopic data and comparing with their reported values in the literature.

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References

- 1 Sartori G, Balini R, Bigi F, Bosica G, Maggi R & Righi P, *Chem Rev*, 104, **2004**, 199 and the references cited therein.
- 2 Anderson M O, Moser J, Sherrill J & Guy R K, *Synlett*, 13, **2004**, 2391 and the references cited therein.
- 3 (a) Subba Rao Y V, Vijayanand P, Kulkarni S J, Subramaniam M & Rama Rao A V, *Syn Commun*, 25, **1995**, 849 (b) Qu L & Bai D, *Org Prep Proceed In*, 31, **1999**, 333 (c) Varma R S, Varma M & Chatterjee A K, *J Chem Soc, Perkin Trans I*, **1993**, 999.
- 4 Ramesh C, Mahender G, Ravindranath N & Das B, *Tetrahedron Lett*, 44, **2003**, 1465.
- 5 Pathak V P, *Syn Commun*, 23, **1993**, 83.
- 6 (a) Goswami A, Kotoky R, Rastogi R C & Ghosh A C, *Org Proc Res Dev*, 7, **2003**, 306; (b) Goswami A, Kotoky R, Rastogi R C & Ghosh A C, *US Patent* **2000**, **6**, **160**, **139**; *Chem Abstr*, 134, **2001**, 17621m.
- 7 Breton G W, *J. Org Chem.*, 62, **1997**, 8952.
- 8 Gould D V, Staeudle H & Hershburg E B, *J Am Chem Soc*, 74, **1952**, 3685.
- 9 Daeben W G & Fonken G J, *J Am Chem Soc*, 76, **1954**, 4618.
- 10 Markar R E, Wagner R B, Ulshafer P R, Wittbecker E L, Goldsmith W D J & Ruof, C H, *J Am Chem Soc* 69, **1947**, 2167.
- 11 Nishiguchi T & Kamio C, *J Chem Soc Perkin Trans 1*, **1989**, 707.

12(a) Nagarajan N & Perumal P, *Chem Lett*, **2004**,1146; (b) Kumar R R, Nagarajan R & Perumal P T, *Synthesis*, **2004**, 949; (c) Nagarajan R & Perumal P T, *Chem Lett* **2004**, 288.

13. Corresponding patent was filed : Goswami A, Das R N & Borthakur N, *Indian Patent, Appl No* 0612/DEL/**2006**.

14 Marvel C S & Rogers J R, *J Polymer Science*, 152, **2003**, 335.

15 Marker R E & Rohrmann I, *J Am Chem Soc*, 62, **1940**, 518.

16 Asolkar L V & Chadha Y R, eds, *Diosgenin and Other Steroid Drug Precursors*, Publication and Information Directorate, CSIR, New Delhi, **1979**, p 92.

17 Hill R A, Kirk D N, Makin H L. J & Murphy G M, eds, *Dictionary of Steroids*, 1st edn, University Press, Cambridge, **1991**, p 169, 802.

18 *The Merck Index*, 11th Edn, **1989**, p 520

19 Bajaj A G & Dev S, *Tetrahedron*, 38, **1982**, 2949,

Table I - Deprotection of alcohols using $\text{KHSO}_4\text{-SiO}_2\text{-MeOH}$ System

No	Substrate	Temp (°C)	Time (H)	Product ^a (Alcohol)A	Product ^b (Ester)B	Yield (%)	m.p./b.p. (°C)(Lit)	Sp.Rot. [α] ₂₅ ²⁵ =(1,CHCl ₃)
1		65	5		AcOMe	A=90	A=202(204)	A=128 ^b (-129)
2		65	2		AcOMe	A=95	A=100(101)	A=-45 (-47)
3		65	8		AcOMe	A=85	A=146(148)	A=-33(-35)
4		65	10		ROMe	A=91 B=71	A=146(148) B=216(218)	A=-6(-9)
5		65	10		AcOMe	A=81	A=147(150)	A=-66 (-66)
6		65	5		AcOMe	A=87	A=160(161)	

)
7	C ₆ H ₅ OAc	RT	1	C ₆ H ₅ OH	AcOMe	A=95	A=179(182)
)
8	3-Ac-C ₆ H ₄ OAc	RT	1	3-Ac-C ₆ H ₄ OH	AcOMe	A=94	A=95(97)
9	4-Ac-C ₆ H ₄ OAc	RT	1	4-Ac-C ₆ H ₄ OH	AcOMe	A=95	A=108(109)
)
10	Me(CH ₂) ₃ OAc	65	5	Me(CH ₂) ₃ OH	AcOMe	A=92	A=115(117)
)
11	C ₆ H ₅ CH ₂ OAc	65	5	C ₆ H ₅ CH ₂ OH	AcOMe	A=89	A=202(205)
)
12	C ₆ H ₁₂ OAc	65	5	C ₆ H ₁₁ OH	AcOMe	A=85	A=159(160)
)
13	C ₆ H ₅ CH(OAc)CH ₃	65	2	C ₆ H ₅ CH(OH)CH ₃	AcOMe	A=93	A=87(88)
14	(CH ₂ OR ₁) ₂ CHOR ₁	65	5	(CH ₂ OH) ₂ CHOH	R ₁ OMe	A=58	A=179(182)
						B=94	B=225(225)
)

R.T = Room temperature. a = Characterized from spectroscopic, sp. rotation and m.p. data that matched with the reported values^{4,14-19}, R=CH₃(CH₂)₇CH=CH(CH₂)₇CO-, R₁=CH₃(CH₂)₅CH(OH)CH₂CH=CH(CH₂)₇CO-

Graphical Abstract

KHSO₄-SiO₂-MeOH-An efficient selective solid supported system for deprotection of alcohols from esters.

KHSO₄-SiO₂-MeOH-efficiently deprotects alcohols from esters through transesterification in methanol.

