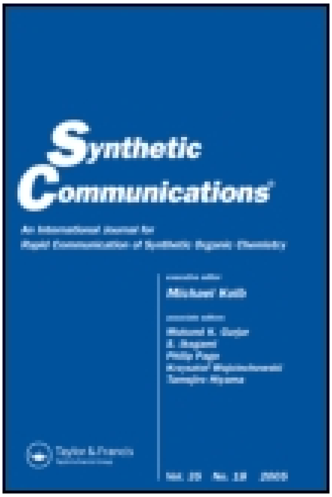

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INFLUENCE OF CATALYST ON THE FORMATION OF 5(10)-ENE KETALS FROM ESTRA-4-EN-3-ONES [#]

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Abstract: The effect of catalyst on formation of isomeric ketals from 19-nor-testosterone and 19-nor-ethisterone is reported. Regioselectivity has been achieved with metal hydrides as catalyst, reported for the first time, to give 5(10)-ene ketals.

In steroids, ketalization is a very useful and well known reaction. Various conditions, mainly acidic, are reported for this purpose[1]. In the case of 19-nor-estra-4-en-3-one derivatives(**1** & **2**) ketalization leads to the formation of two isomeric products(**3** & **4**). The present study was aimed at the preparation of 5(10)-ene ketals for which various catalysts and reaction conditions have been tried.

Ketalization of 19-nor-testosterone(**1**) and 19-nor- ethisterone(**2**) with ethylene glycol was carried out in the usual manner by refluxing the two reactants in a solvent in presence of a catalyst. Yields of the ketals formed and their isomeric

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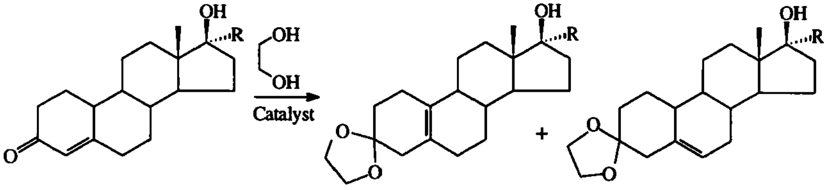

1; R = H
2; R = - C≡CH

3

4

R = H/ - C≡CH

ratio are shown in the table. Acid catalyzed reactions with *p*TSA, conc. H_2SO_4, and Amberlyst-15 gave a mixture of isomeric ketals **3** & **4**, which were separated by column chromatography and their identity established on the basis of NMR studies. The two isomers were obtained in equal ratio. A significant increase in the formation of the isomer **3** was observed when chlorotrimethylsilane(CTMS) was used as a catalyst[2,3]. In order to have a bulkier group on the silane, which is known to form a complex with the carbonyl group[4] and may have directing influence on the positioning of the double bond, t-butyldimethylsilylchloride(TBSC) was tried. This led to a further increase in the formation of the desired isomer(80%). Use of t-butyldiphenylsilylchloride did not lead to any further improvement. Increasing the molar proportion of the catalyst in all these cases did not help to change the isomeric ratio.

On changing the reaction conditions to base catalyzed ketalization, there was a dramatic influence on the isomeric ratio. Use of potassium t-butoxide in t-butanol produced isomers in 90:10 ratio in a relatively short time in good yield. When the ketalization reaction was performed in the presence of a metal hydride(CaH_2/NaH) in benzene, it led to an exclusive formation of isomer **3**. However, the yields obtained in these cases were low. When the higher boiling solvent xylene was used in the CaH_2 catalyzed reaction, it led to formation of a mixture of isomers which were characterized[5]. The use of metal hydride in ketalization is reported for the first time.

Table: Influence of catalyst on isomeric ratio of ketals during ketalization.

Compd	Catalyst	Mol.ratio of catalyst	Solvent	Rn.time hr.	Temp °C	Yield %(a)	Ketals 3 : 4
1	*p*TSA	0.286	Benzene	10	80	56	50:50
2	*p*TSA	0.252	Benzene	10	80	49	50:50
1	H_2SO_4	---	Benzene	5.5	36	48	50:50
1	Amberlyst-15	---	Benzene	6	80	52	50:50
2	Amberlyst-15	---	Benzene	6	80	43	50:50
1	CTMS	2.33	Benzene	8	80	59	70:30
2	CTMS	2.33	Benzene	8	80	52	66:34
1	TBSC	1.19	Benzene	8	80	49	80:20
2	TBSC	1.19	Benzene	8	80	43	78:22
1	t-BuOK	2.70	t-BuOH	2	82	78	90:10
2	t-BuOK	2.54	t-BuOH	2	82	90	90:10
1	CaH_2	20	Benzene	5	80	28	100:0
2	CaH_2	20	Benzene	6	80	30	100:0
1	NaH	28.3	Benzene	6	80	22	100:0
2	NaH	28.3	Benzene	6	80	20	100:0

a. Refers to an isolated yield in which unreacted product accounts for the rest of the material.

Experimental Section:

General Procedure for ketalization using *p*TSA/ H_2SO_4/ Amberlyst-15/ CTMS/TBSC as catalyst:

A mixture of the ketone and ethylene glycol in 1:1.5 molar ratio , catalyst and molecular sieves was refluxed in dry benzene using Dean- Stark apparatus. Reaction mixture was washed with 10% $NaHCO_3$ solution , extracted with dichloromethane and dried over anhydrous Na_2SO_4. The solvent was distilled off and the residue was chromatographed over neutral alumina using benzene- ethyl acetate as eluant to give the ketal.

General procedure for ketalization using t-BuOK as catalyst:

A mixture of the ketone and ethylene glycol in 1: 1.5 molar ratio, t-BuOK and molecular sieves was refluxed in t-BuOH . Reaction mixture was poured into water, extracted with dichloromethane and processed as above.

General procedure for ketalization using CaH_2/ NaH as catalyst.

A mixture of the ketone and ethylene glycol in 1 : 1.5 molar ratio, catalyst and molecular sieves was refluxed in dry benzene. The reaction was poured into water and processed as above.

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References & Notes:

1. Meskens,F.A.J.; *Synthesis*,**1981**, 501.
2. Chan,T.H.; Brook,M.A.; Chaly,T.; *Synthesis*, **1983**, 203.
3. Tandon,A.; Ray,S.; *Indian J. Chem.*, **1992**, 31B, 58.
4. Verma,P.; Ray,S.; *Indian J. Chem.*, **1990**, 29B, 652
5. Ketal **3**(R=H): mp,111-13°(115°)[6], ^{1}HNMR(400Hz,$CDCl_3$):δ0.76(s,3H,18-CH_3),2.30(s,1H,10CH),3.64(t,1H,17-CH,J=9.2Hz),3.96(s,4H, CH_2-CH_2 of ketal group). Mass: 318(M^+).

Ketal **4**(R=H):mp,136-137^0(mp:137.5-39°)[7]; ^{1}HNMR(400Hz,$CDCl_3$):δ 0.80 (s,3H,18-CH_3), 3.65(t,1H,17-CH,J=9.2Hz), 4.0(s,4H,CH_2-CH_2 of ketal group), 5.48(bs,1H,6-CH); Mass: 318(M^+).

Ketal **3**(R=-C≡C-H):mp:156-58°(146-49°)[8];^{1}HNMR(400Hz,$CDCl_3$):δ 0.86(s,3H,18-CH_3), 2.32(s,1H,10-CH), 2.56(s,1H, -C≡C-H), (s,4H,CH_2-CH_2 of ketal group); Mass: 342(M^+).

Ketal **4**(R= -C≡C-H): mp:173-76° (178°)[9]; ^{1}HNMR(400Hz, $CDCl_3$): δ 0.82(s,3H,18-CH_3), 2.30(s,1H,19-CH), 2.58(s,1H,-C≡C-H), 4.0(s,4H, CH_2-CH_2 of ketal group);Mass: 342(M^+).

6. Roussel-UCLAF *Neth. Appl.*6,603,268 (C1,C07c),Sept.19,**1966**. **Chem. Abstr.** 66:P 65718x.

7. Frank B. Colton (to G.D. Searle & Co.) *US* 2,946,809,July26,**1960.Chem. Abstr.**54:P22733e

8. *Japan*, 16299(67)(C1,16D611), Sept.4, Appl. Oct.29,**1964**,7PP.**Chem. Abstr.**68:P114829m.

9. Hofmeister,H.;Laurent,H.;Schulze P.E.;Annen K.;Pollow K.; Grill,H.J.(Schering A-G) *Eur. Pat. Appl. EP* 137434(Cl.C07J1/00), 17 April **1985,Chem. Abstr.**103:P215643t.

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