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G. M. Caballero [a] & E. G. Gros [a]
[a] Departamento de Quimica Orgánical, Facultad de Cencias Exactas y Naturales , Universidad de Buenos Aires Pabellon 2, Ciudad Universitaria , 1428 Buenos Aires, Argentina
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CLEAVAGE OF ACETALS PROMOTED BY COPPER (II) SULPHATE ADSORBED ON SILICA GEL

Gerardo M. Caballero and Eduardo G. Gros *

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellon 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

Abstract. Copper sulphate supported on silica gel promotes the easy removal of cyclic acetals and tetrahydropyranyl ethers to give the respective parent carbonyl and hydroxyl compounds.

The temporary masking of hydroxyl and carbonyl functions by preparation of their tetrahydropyranyl ethers and acetals respectively has been applied widely. Most of the methods used for the cleavage of these protective groups employ aqueous reaction media acidified with mineral acids, or non-aqueous media acidified with organic acids such as p-toluenesulphonic acid[1]. There are few examples which make use of non-aqueous neutral reaction conditions[2]. Even lesser are the cases of cleavage methods performed with the reagent deposited on an inorganic support such as the one which uses iron (III) chloride adsorbed on silica gel[3].

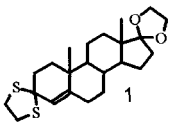
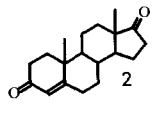
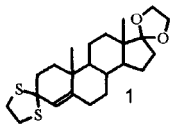
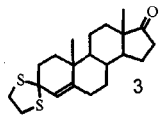
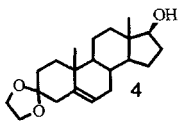
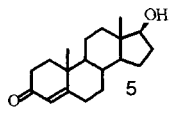
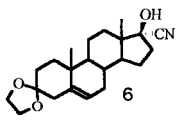
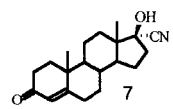
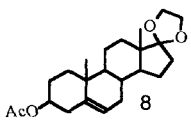
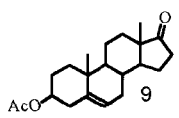
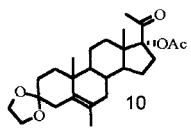
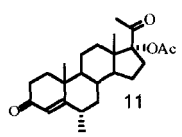
As an extension of our previous work on removal of thioacetals [4], we report here that copper (II) sulphate supported on silica gel in organic solvents promotes, under mild conditions, the removal of acetals and tetrahydropyranyl ethers leading to the parent carbonyl and hydroxyl bearing compounds respectively.

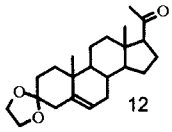
RESULTS AND DISCUSSION

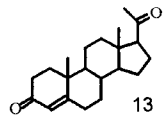
Several cycloacetals and tetrahydropyranyl ethers derivatives were submitted to the action of silica gel-supported copper (II) sulphate in organic solvents at different temperatures affording,

* To whom correspondence should be addressed.

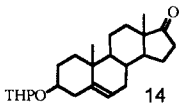
Table 1. Cleavage of acetals by copper (II) sulphate adsorbed on silica gel.

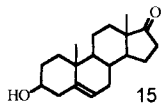
SUBSTRATE	PRODUCT	SOLVENT	T °C	t (h)	%
 1	 2	benzene	80	5	90
 1	 3	dichloromethane	40	4	95
 4	 5	chloroform	60	3	82
 6	 7	chloroform	60	4	61 [a]
 8	 9	chloroform	60	5	93 [b]
 10	 11	chloroform	60	2	81 [b]



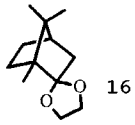


chloroform	60	24	85 [b]

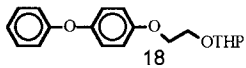


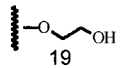


dichloromethane	40	24	70 [c]

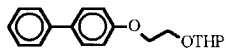


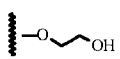
chloroform	20	48	70 [a]





chloroform	60	18	80 [b]





chloroform	60	16	78

Gramms of reagent/mmol substrate, a: 2.0, b: 2.5, c: 3.5

after chromatographic purification, the respective parent carbonyl and hydroxyl compounds. The results are summarized in Table 1.

From the data it is evident that the present procedure is useful for the removal of cycloacetals and tetrahydropyranyl groups when the reactions are performed in solvents of low polarity such as dichloromethane, chloroform or benzene. More polar solvents, like tetrahydrofuran, ethyl acetate or acetone, which were also tested, completely inhibited the reagent's activity. It can be observed that, under appropriate conditions, the method allows chemoselective removal of cycloacetals in the presence of cyclothioacetals and does not affect neither cyanohydrin and ester functions nor primary and sterically hindered secondary alcohols. The reaction conditions must be carefully controlled when the product is expected to be a sterically unhindered secondary alcohol, as it is known that the reagent may lead to dehydration of substrates[5].

The reagent was applied to the doubly protected steroid derivatives **22**, **23** and **24** in order to check its capability as promotor of regioselective remotion of cycloacetals or tetrahydropyranyl groups on different positions of the steroid ring system. Results are shown in Fig. 1 and Table 2. The result with the bis-cycloacetal **22** indicates that the cycloacetal moiety on C-17 is more easily removed than the one on C-3; this result is opposite to that observed for acetal cleavage reactions in a homogeneous phase[6]. Regarding the regioselectivity of the method, no satisfactory results were obtained indicating that the reactivities of the tetrahydropyranyl and cycloacetal groups are very similar. An analogous behaviour is reported for these protecting groups in the presence of $FeCl_3$-SiO_2[3]. Some representative spectroscopic data of the substrates and of some products are presented in Table 3.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer (at 100.1 and 25.2 MHz respectively) operating in the FT mode. Direct inlet mass spectra were obtained with a Varian-MAT CH7-A spectrometer operating at 70 eV. Gas chromatography-mass spectrometry analyses were done on a Trio-2/2000 VG Masslab spectrometer coupled with a Hewlett-Packard 5890 Series 2 gas chromatograph equipped with a DB-5 capillary column (15 m x 0.25 mm). Gas chromatography analyses were done on a Hewlett-Packard 5890 gas chromatograph with HP-5 and HP-101 capillary columns.

Preparation of acetals.

Method A[7]. A solution of the carbonyl compound (1 mmol) in benzene (20 ml) and ethyleneglycol (5 ml) was refluxed for 24 h collecting water in a Dean-Stark trap. p-TsOH (2 mg) was added and the mixture refluxed further for 24 h. The reaction mixture was washed with $NaHCO_3$ (10%) and water, dried ($MgSO_4$) and evaporated to yield the crude material which was purified by column cromatography (silica 40-63) eluted with the mixture of solvents indicated in each case.

3-Cycloethylenedithio-17-cycloethylenedioxy-androst-4-ene (**1**). Purification, hexane:EtOAc (85:15). Yield, 66% (using method B the yield was 87%). m.p. 104-107°. Found: C, 67.90; H, 8.38; S, 15.72. Calculated for $C_{23}H_{34}O_2S_2$: C, 67.84; H, 8.43; S, 15.77 %.

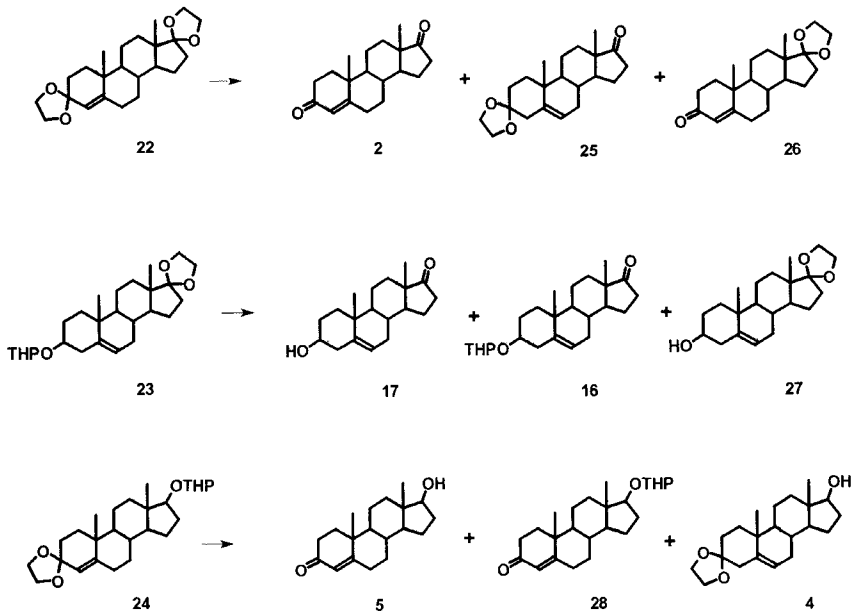


Fig. 1

Table 2. Reactions of substrates 22, 23, and 24 with silicagel-adsorbed copper(II) sulphate.

Substrate	Solvent	time (h)	temp (°C)	ratio*	Product and yield (%)			
22	$CHCl_3$	24	25	2.0	**2** (12)	**25** (42)	**26** (traces)	**22** (40)
23	$CHCl_3$	40	25	3.0	**17** (51)	**16** (30)	**27** (6)	**23** (<1)
23	benzene	40	25	3.0	**17** (17)	**16** (2)	**27** (59)	**23** (13)
24	$CHCl_3$	16	25	3.0	**5** (57)	**28** (4)	**4** (10)	**24** (<1)
24	benzene	16	25	3.0	**5** (2)	**28** (4)	**4** (19)	**24** (40)

* gramms reagent/mmol substrate

Table 3. Spectroscopic data of substrates and selected products (δ values).

	^{1}H-NMR				^{13}C- NMR			
Comp.	**H-4**	**H-6**	**H-18**	**H-19**	**C-3**	**C-17**	**C-18**	**C-19**
1	5.49	-	0.86	1.02	65.7	119.0	14.3	18.6
3	5.53	-	0.88	1.04	65.5	220.5	13.7	18.5
4	-	5.34	0.78	1.05	109.2	81.5	11.0	18.9
6*	-	5.34	0.88	1.04	109.2	80.6	12.1	18.9
7	5.76	-	0.92	1.20	199.7	80.6	12.2	17.4
8	-	5.38	0.87	1.03	73.8	119.2	14.1	19.3
10	-	-	0.60	0.97	109.6	-	14.2	19.5
12	-	5.36	0.64	1.04	109.2	63.5	13.1	18.8
16	-	5.39	0.88	1.04	75.7	220.2	13.5	19.3
22	-	5.36	0.87	1.04	109.1	119.2	14.1	18.8
23	-	5.38	0.88	1.04	75.8	119.3	14.1	19.3
24	-	5.35	0.81	1.04	109.1	86.3	11.5	18.8
25	-	5.38	0.89	1.05	109.1	220.5	13.5	18.9
27	-	5.38	0.88	1.03	71.5	119.3	14.2	19.4
28	5.73	-	0.82	1.20	199.2	86.3	11.7	17.4

* Data of the 17α -CN epimer. All data obtained in $CDCl_3$.

3-Cycloethylenedioxy-androst-5-ene-17β-ol (**4**).Purification, hexane:EtOAc (70:30). Yield, 82%. m.p. 162-164° (lit.[8] 183-184° MeOH).

Method B[9]**.** A suspension of the carbonyl compound (1 mmol) in ethyleneglicol (3 ml) and ethyl orthoformate (2 ml), treated with p-TsOH (cat. amount), was stirred at 40 °C for the time indicated in each case. $NaHCO_3$ (10%) was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to obtain the crude material that was purified by column chromatography (silica gel 40-63) eluted with the mixture of solvents indicated in each case.

3β-Acetoxy-17-cycloethylenedioxy-androst-5-ene (**8**). Reaction time, 3 h; purification, hexane: EtOAc (83:17). Yield, 77%. The analytical sample was recristalized from MeOH, m.p. 135-137° (lit.[10] 137-139° MeOH).

3-Cycloethylenedioxy-6-methyl-17α-acetoxy-pregn-5-ene-20-one (**10**). Reaction time, 72 h; purification, hexane:EtOAc (80:20). Yield, 46%. m.p. 180-183° (lit.[11] 185-187° acetone-petroleum ether).

3-Cycloethylenedioxy-pregn-5-ene-20-one (**12**). Reaction time, 6 h; purification, hexane:EtOAc (85:15). Yield, 77%. m.p. 178-180° (lit.[12] 180-181° acetone-hexane).

3,17-Bis-cycloethylenedioxy-androst-5-ene (**22**). Reaction time, 3 h; purification, hexane:EtOAc (80:20). Yield, 71%. The analytical sample was recristalized from MeOH, m.p. 167-170° (lit.[13] 165-172.5 MeOH).

2-Cycloethylenedioxy-camphor (**16**). Reaction time, 24 h; purification, hexane:EtOAc (90:10). Yield, 88%. Found: C, 73.37; H, 10.18. Calculated for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27 %.

^{1}H NMR, δ (ppm): 0.79 (3H,s,Me-10); 0.83 (3H,s,Me-8); 1.01(3H,s,Me-9); 3.84 (4H,m, -O(C**H**$_2$)$_2$O-).

^{13}C NMR, δ (ppm): 9.7 (C-10); 20.3 (C-8 and C-9); 26.8 (C-5); 29.3 (C-6); 44.5 (C-7); 44.8 (C-4); 47.9 (C-3); 52.0 (C-1); 63.5 and 64.7 (-O(**C**H$_2$)$_2$O-); 116.8 (C-2).

Preparation of 6.

3-Cycloethylenedioxy-androst-5-ene-17-one (**25**). A solution of androst-4-ene-3,17-dione (**2**) (920 mg) and a catalytic amount of p-TsOH in freshly prepared 2-ethyl-2-methyl-1,3-dioxolane (17 ml) , was slowly distilled for 5 h until 10 ml of distillate were obtained. Benzene was added to the reaction mixture and the resulting organic layer was washed with $NaHCO_3$ (5%) and water, dried ($MgSO_4$) and evaporated to yield 960 mg of an oil. This oil was purified by column chromatography (silica gel 40-63) eluted with hexane:EtOAc (85:15) to yield 408 mg of compound **22** and then with hexane:EtOAc (75:25) to give 380 mg of compound **25** of m.p. 196-197° (lit.[8] 197-198 °).

17ξ-Cyano-17ξ-hydroxy-3-cycloethylenedioxy-androst-5-ene (**6**). To a suspension of compound **25** (380 mg) and KCN (900 mg) in absolute alcohol (15 ml) , AcOH (2.4 ml) was added dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 48 h. After addition of $NaHCO_3$ (10%), the mixture was extracted with CH_2Cl_2 and the organic layer was washed with water, dried ($MgSO_4$) and evaporated to obtain 390 mg of crude material which was purified by column chromatography (silica gel 60, hexane:EtOAc 70:30), yielding 340 mg (83%) of the epimeric mixture (17α-CN : 17β-CN = 4.5 : 1 as determined by ^{1}H NMR spectroscopy). m.p. 167-171° (lit.[9] 169-172° EtOH).

Preparation of tetrahydropyranyl ethers[14]. To a solution of 1 mmol of the hydroxy compound in anhydrous CH_2Cl_2 (7 ml), dihydropyrane (0.2 ml) and pyridinium *p*-toluenesulfonate (catalytic amount) were added. The mixture was stirred at room temperature for 20 h and CH_2Cl_2 (10 ml) was added. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to yield the crude product which was purified as indicated.

3β-O-(Tetrahydropyranyl)-androst-5-ene-17-one (**14**). Purified by crystalization from MeOH. Yield, 96%. m.p. 173-175° (lit.[15] 174-176°).

3-Cycloethylenedioxy-17β-O-(tetrahydropyranyl)-androst-5-eno (**24**). From compound **4** (160 mg) a crude mixture (210 mg) was obtained. This was purified by column chromatography (silica gel 60) eluted with hexane:EtOAc (85:15) to obtain the title compound (75 mg, 38% yield) of m.p. 150-155° (lit.[16] 153-173° Cl_2CH_2-MeOH with 1% Py) and *17β-O-(tetrahydropyranyl)-androst-4-ene-3-one* (**28**) (55 mg, 31%) of m.p. 98-100° (lit.[15] 102-104° pentane).

Preparation of 23.

17-Cycloethylenedioxy-3β-hydroxy-androst-5-ene (**27**). To a solution of compound **8** (280 mg, 0.74 mmol) in THF (20 ml) , $LiAlH_4$ (100 mg) was added and the mixture was stirred under a nitrogen atmosphere, at room temperature for 1 h. The reaction was carefully quenched by addition of EtOAc and the solution washed with sodium-potassium tartrate (10%) and water, dried ($MgSO_4$) and evaporated to obtain 260 mg of the crude material; this was purified by column chromatography (silica gel 60) eluted with hexane:EtOAc (55:45) yielding 200 mg (80%) of pure **27**. The analytical sample was recristalized from acetone, m.p. 163-165° (lit.[17] 166° acetone).

3β-O-(Tetrahydropyranyl)-17-cycloethylenedioxy-androst-5-ene (**23**). Following the general procedure for preparation of tetrahydropyranyl ethers, compound **27** was converted into compound **23**. Purification, column chromatography (silica gel 60) eluted with hexane:EtOAc (90:10). Yield, 77%. m.p. 130-135° (lit.[16] 135-139° Cl_2CH_2-MeOH with 1% Py).

Preparation of the reagent. As described in literature[4].

Cleavage of the Protecting Group. General Procedure. In a typical experiment the substrate (1 mmol) was treated with the reagent (3.0 g; 3.3 mmol $CuSO_4$, unless otherwise indicated in Table 1) in 30 ml of the appropriate solvent. The progress of the reaction was monitored by TLC

or GC. The product was isolated by filtration and evaporation of the solvent. The yields were calculated by weighing the pure (GC-MS) products.

The products showed consistent melting points and spectroscopic data (^{1}H and ^{13}C NMR spectra) identical to those of authentic samples[18].

In the cases of substrates **22**, **23** and **24** the reactions were monitored by GC and co-injection with authentic samples of the products. The respective mixture was chromatographed on silica gel 60 column eluting with hexane-EtOAc mixtures of increasing polarity. The isolated products were characterized by comparison (mp, ^{1}H and ^{13}C-NMR spectra) with authentic samples.

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18. Samples of substrates **18** and **20**, as well as products **19** and **21**, were kindly provided by Dr. J. B. Rodriguez and their preparation and spectroscopic data are described elsewhere[19].

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