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DEPROTECTION OF CARBONYL GROUPS BY ANODIC OXIDATION OF DITHIOACETALS : A KEY STEP IN THE SYNTHESIS OF α-DIONES, α-KETOLS AND CHIRAL SYNTHONS.

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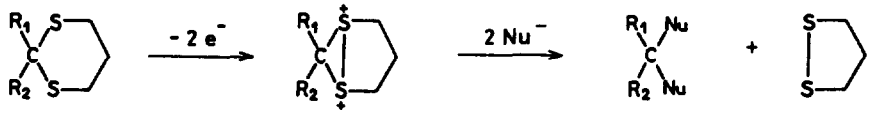
Summary : *The anodic oxidation of α-keto and α-hydroxythioacetals provides an efficient way for the regeneration of α-diones and α-ketols, specially in the cases where chemical reactions are unsuccessful.*

Some syntheses of the natural pheromone brevicomin require chiral α-diols as starting materials. The most convenient way for obtaining such synthons involves the removal of dithian protecting groups in α-oxo or α-hydroxythioacetals. The synthesis of these latter compounds has been previously reported (1-3) but the regeneration of the carbonyl group is extremely difficult and even unsuccessful whatever the chemical method (4-9) when the synthesis of brevicomin is involved.

During the past fifteen years, some papers (10-14) have described the ability of electrochemistry to perform the deprotection of carbonyl groups through the direct or indirect anodic oxidation of dithioacetals according to the following scheme :



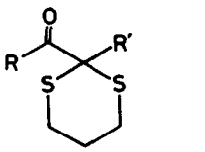
If water is used as nucleophile, the unstable gem-diol which is formed leads to the regeneration of the carbonyl function.

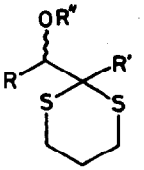
In the present work we report our results on the anodic reactivity of α-ketothioacetals and related compounds (1a - 1c , 2a - 2c and 3) and their transformation into the corresponding α-diones and α-ketols.

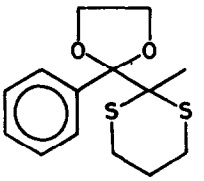
These examples show the advantages of electrochemistry in two main fields :

- the deprotection of dithioacetals even possessing in their vicinity a function having a strong electron-withdrawing effect (compounds 1a to 1c);

- the selectivity of the method when two different protecting groups are present in the same molecule (compound 3).





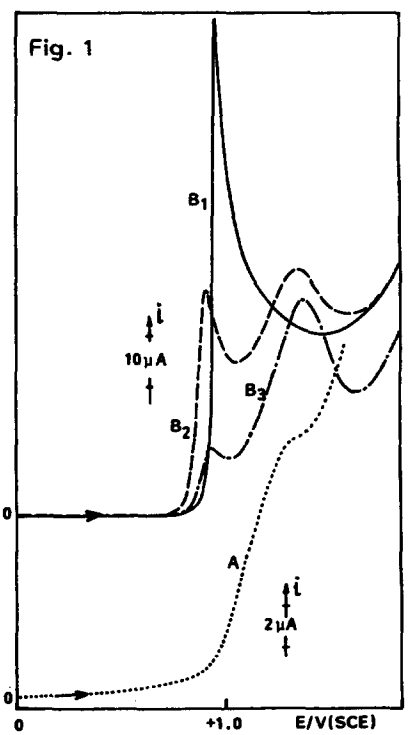


1a : R=C_2H_5 R'= 
1b : R=CH_3 R'=C_2H_5
1c : R=CH_3 R'=C_6H_5

2a : R=C_2H_5 R'=H R''=Bz
2b : R=CH_3 R'=C_2H_5 R''=H
2c : R=C_6H_5 R'=CH_3 R''=H

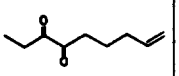
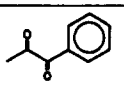
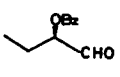
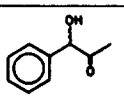
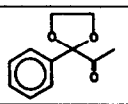
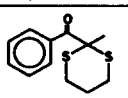
3

The oxidation of 1a to 1c carried out on a platinum anode in wet acetonitrile (10 % V/V of H_2O) occurs at very positive potentials due to the presence of the carbonyl group in the α-position of the thioacetal ring. The voltammogramm at a stationnary electrode presents (Fig. 1, curve A) an ill-defined oxidation peak (E_p = + 1.35 V/SCE) close to the anodic discharge of the supporting electrolyte. Voltammetric controls monitored during macroscale electrolyses on a platinum foil used as working electrode at 1.20 V/SCE show no decrease of the peak intensity. This fact can be certainly due to the presence of electroactive species formed during the removal of the protecting group (in particular the disulfide S — S) which can be oxidized at a potential quite close to that of the starting material. The amounts of electricity consumed are always higher than 2 F.mole^{-1}. The excess can be explain by the oxidation of organic side-products. All our experiments have been stopped after an electricity consumption corresponding to 2.5 F.mole^{-1}. It can be also noted that a fast inhibition of the working electrode requires periodic pulsing to 0 Volt during about thirty seconds to maintain the current at its initial value.



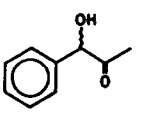
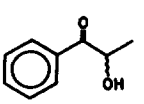
A: Oxidation of 1a (6 mmol.dm^{-3})
B: Oxidation of 2b(13 mmol.dm^{-3})
B1: before electrolysis
B2: after consumption of 1.1 F.mol^{-1}
B3: after consumption of 2.0 F.mol^{-1}

On the contrary, compounds 2a to 2c are more easily oxidized (+ 1.0 V/SCE). The voltammogramms show a single sharp oxidation step (Fig. 1 curve B1). Cyclic voltammogramms scanned during a macroelectrolysis indicate the progressive appearance of a second oxidation peak (Fig 1 curves B2 and B3) located at a more positive potential (E_p = + 1.35 V/SCE). This step can be due to the oxidation of a neutral electroactive species, a disulfide in this case. The whole substrate is oxidized after consumption of 2.2 $F.mole^{-1}$. Details of the electrolyses conditions and the results are summarized in the table.

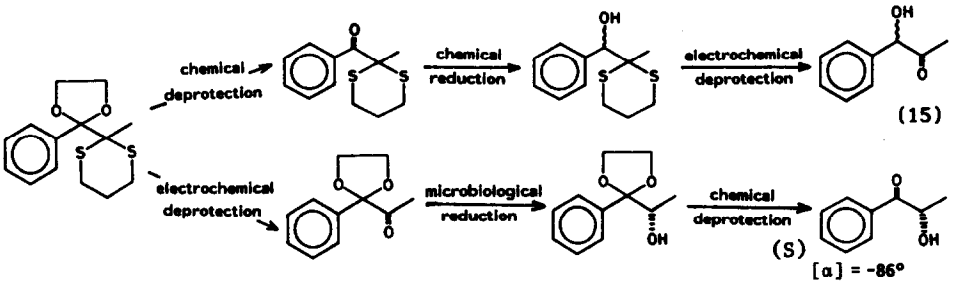
Substrates	Products	isolated yield (%)	$[\alpha]^{25}_{578}$ $CHCl_3$	E V/SCE	NMR δ_{ppm} relative to TMS
1a		(70)		1.30	1.1(t,3H) 1.8-2.1(m,6H) 2.9(q,2H) 4.9-5.2(m,2H) 5,6-6,1(m,1H)
1b		(80)		1.35	1.1(t,3H) 2.35(s,3H) 2.8(q,2H)
1c		(82)		1.30	2.5(s,3H) 7.6-8.1(m,5H)
2a		(60)	+41° (c=0,07)	1.05	1.1(t,3H) 3.6(m,1H) 4.7(m,2H)
2b		(70)	+48° (c=0,09)	1.00	1.1(t,3H) 1.4(d,3H) 2.55(q,2H) 4.2(m,1H)
2c		(85)		1.00	2.1(s,3H) 5.2(s,1H) 7.5(s,5H)
3		(70)		1.05	2.1(s,3H) 3.8-4.1(m,4H) 7.2-7.8(m,5H)
3		(100)		chemical way *	1.8(s,3H) 2.2-3.1(m,6H) 7.3-8.2(m,5H)

* : *according to the procedure reported in (7).*

Electrochemistry can also be a selective method for the removal of protecting groups. Coupled with more classical reactions used in organic chemistry, anodic oxidations permit to obtain, in our case, the isomeric ketols :

 and 

according to the following scheme :



Consequently, these results prove that electrochemistry is the most convenient method for deprotection of scarcely reactive dithioacetals. The regioselectivity and the mildness of the oxidation process allow the synthesis of α-ketols isomers.

Preparative scale electrolyses :

Macroscale electrolyses were performed in a conventional three compartments H-cell with amounts of thiocetal varying from 2.5 to 10 mmoles solubilized in 100 ml of the anolyte. After electrolysis, the solution is diluted with 300 ml of water and the reaction product extracted with ether. The solvent is then evaporated and the crude residue purified by chromotography on silica (eluent pentane - ether 90/10).

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