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CHEMOSELECTIVE ELECTROLYTIC CHLORINATION OF METHYL GROUP OF 3-METHYL-3-BUTENOATE MOIETY OF THIAZOLINE-AZETIDINONE HOMOLOGUES

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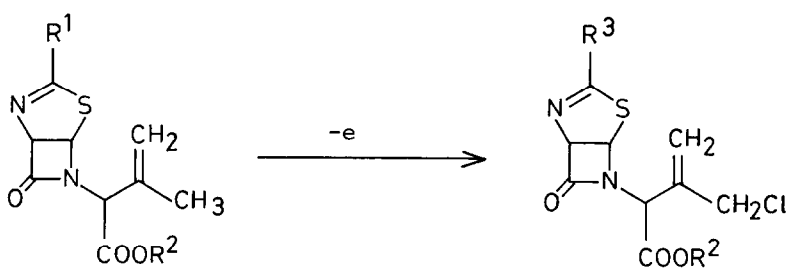
ABSTRACT: Chemoselective electrochlorination of the methyl group on the 3-methyl-3-butenoate moiety of thiazoline-azetidinone derivatives derived from penicillins G and V has been performed in a CH_2Cl_2-H_2O-NaCl-H_2SO_4-(Pt or C electrodes) system by adjusting the amount of electricity passed as well as the concentration of Cl^- in the media.

Synthetic approaches to cephalosporin antibiotics by the conversion of readily available penicillins have proved to be the most fruitful ones. [1] Especially, thiazoline-azetidinone derivatives 1 [2] have been used as key intermediates for the penicillin-cephalosporin conversion in which the oxidative functionalization of the methyl group of the 3-methyl-3-butenoate moiety is an essential step. [3] Recently, Cooper reported the direct chlorination of 1 with chlorine (25 °C, 3 days) or t-butyl hypochlorite (~60% yields), giving the corresponding chlorinated compounds 2, bearing benzyl, phenyl, p-tolyl, and phenoxymethyl groups as the R^3 substituents. [3a,b]



1 2

During our studies on halide salts promoted electrosynthesis [4] we found that electrolysis of 1 (R^1 = $PhCH_2$, $PhCCl_2$, $PhOCH_2$, and PhC=O) in two-phase systems (H_2O-CH_2Cl_2-Pt or C electrodes) provided chemoselective electro-chlorination products 1g (R^1 = $PhCCl_2$) and 2a-f, depending on the amount of electricity passed as well as on the concentration of Cl^- in the media.

A typical electrochemical trichlorination procedure of 1a (R^1 = $PhCH_2$, R^2 = Me) is as follows: A stirred mixture of thiazoline-azetidinone 1a (400 mg), NaCl (8g), and H_2SO_4 (0.5 ml) in H_2O (24 ml)-CH_2Cl_2 (20 ml) was electrolyzed by using platinum foil electrodes (anode 6 cm^2) in an undivided cell at a constant current (10 mA/cm^2) at room temperature. After passing 15 F/mol of electricity, the organic phase was separated and the usual workup followed by column chromatography (SiO_2, benzene-AcOEt; 5/1) gave 2a (R^3 = $PhCCl_2$, R^2 = Me) in 89% yield: mp 97.5-98.5 °C (from AcOEt-hexane); IR ($CHCl_3$) 1780, 1745, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.81 (s, 2H), 5.14 (s, 2H), 5.41 (s, 1H), 6.05 (m, 2H), 7.30-7.90 (m, 5H).

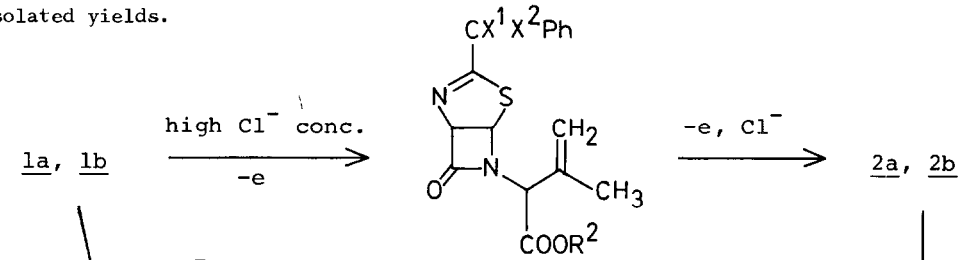
Likewise, the electro-chlorination of 1b-e proceeded smoothly, yielding the corresponding allylic chlorides 2b-d. The results are summarized in the Table. Carbon electrodes can be used without any disadvantage (entry 2). The effect of H_2SO_4 was remarkable, since the absence of H_2SO_4 resulted in a mixture of benzylic chlorides 1g (25%), 1h (20%), and recovered 1a (34%) together with complex compounds (20%) after passage of 15 F/mol of electricity. Particularly noteworthy is the fact that the two-phase electrolysis procedure brought about no appreciable amount of hydrolysis products on either the thiazoline or the β-lactam ring. In place of CH_2Cl_2, other hydrophobic solvents, e.g., $CHCl_3$ and AcOEt, could be used. However, the use of hydrophylic solvents, e.g., THF, CH_3CN, CH_3CN-THF, or CH_2Cl_2-THF, even in a two phase system, facilitated hydrolysis of the thiazoline and/or the β-lactam ring, leading to the ring opened products 3 and/or 4.

In the course of electro-chlorination of 1b (R^1 = $PhCH_2$), leading to trichlorides 2b (entry 3), gem-dichloride 1c (89%) was obtained as an initial product at a higher concentration of sodium chloride (1g/3 ml) in water when 10 F/mol of electricity was passed. Electrolysis of the dichloride 1c in the same media afforded 2b in 85% yield (entry 4). The result is in contrast to that of the electrolysis at a lower concentration of aqueous sodium chloride (100 mg/3 ml), which gave rise to the competitive formation of benzylic and allylic chlorides 1c (9%), 1f (11%), 2e (10%), and 2f (11%). This change of the product distribution is due to

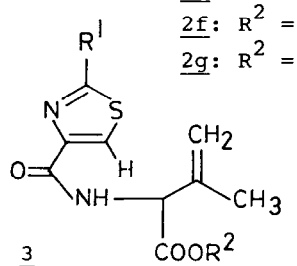
Table Electro-chlorination of Thiazoline-azetidinones[a)]

entry	substrate 1			electrolysis system	electricity F/mol	product 2		
		R^1	R^2			R^3	(Yield, %)[b)]	
1	1a	$PhCH_2$	Me	H_2O-CH_2Cl_2-(Pt)	15	2a	$PhCCl_2$	(89)
2	1a	$PhCH_2$	Me	H_2O-CH_2Cl_2-(C)	15	2a	$PhCCl_2$	(82)
3	1b	$PhCH_2$	$PhCH_2$	H_2O-$CHCl_3$-(Pt)	25	2b	$PhCCl_2$	(76)
4	1c	$PhCCl_2$	$PhCH_2$	H_2O-$CHCl_3$-(Pt)	10	2b	$PhCCl_2$	(85)
5	1d	$PhOCH_2$	Me	H_2O-CH_2Cl_2-(Pt)	10	2c	$PhOCH_2$	(77)
6	1e	PhCO	Me	H_2O-CH_2Cl_2-(Pt)	5	2d	PhCO	(80)

a) Carried out at a constant current of 10 mA/cm^2 at room temperature.
b) Isolated yields.



2e: R^2 = $PhCH_2$; X = H
2f: R^2 = $PhCH_2$; X = Cl
2g: R^2 = Me; X = H



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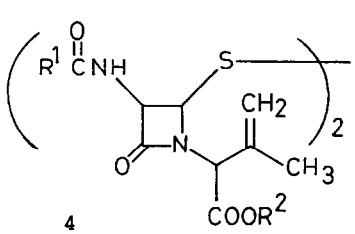

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the fact that the discharge of Cl^- can produce different chlorinating agents, e.g., Cl_2, HOCl, $HClO_2$, etc., depending upon the Cl^- concentration, the pH, and the oxidation potentials in the media.[5] Conversion of 2a and 2b ($R^3 = PhCl_2$) into the corresponding allylic chlorides 2e and 2g ($R^3 = PhCH_2$) can be achieved in over 90% yields by removal of the chlorine atoms attached to the benzyl carbon by treatment with zinc dust in AcOH-CH_2Cl_2 (1/4) at 0-2 °C.

The extention of this versatile electro-chlorination reaction is in progress and will be reported in due course.

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