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ELECTROCHEMICAL S-S BOND FISSION OF 4-(2-BENZOTHIAZOLYLDITHIO)AZETIDINONES (KAMIYA'S DISULFIDES)[1)]

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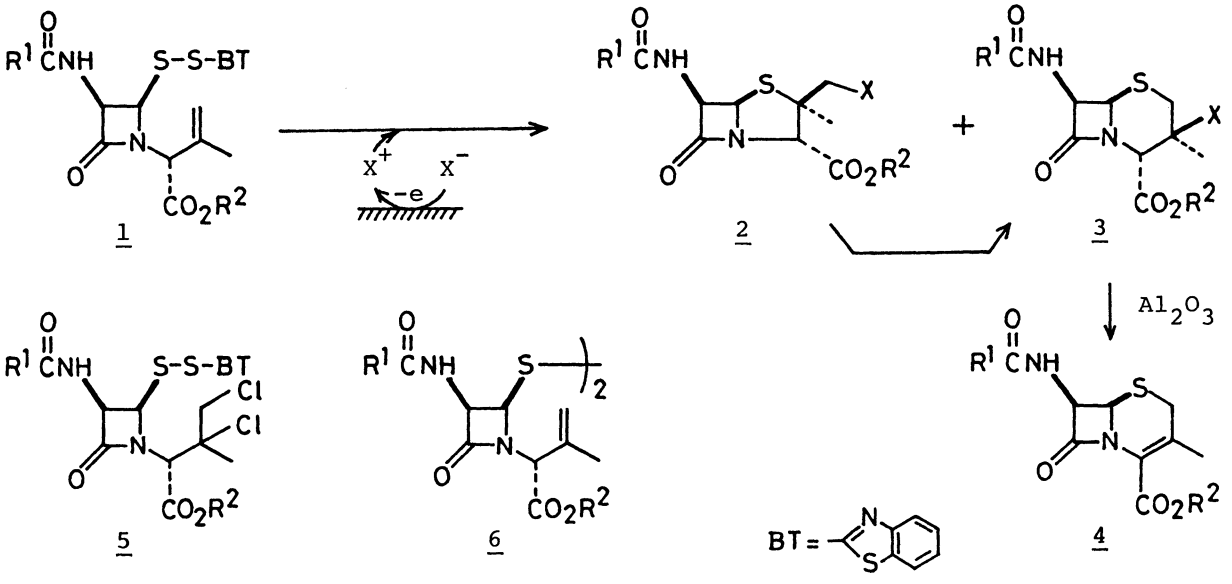
An electrochemical S-S bond fission of 4-(2-benzothiazolyldithio)azetidinones derived from penicillin G has been achieved by the selection of an appropriate electrolysis system, providing either 2β-halomethylpenicillins, 3β-halocephams, or 4-methoxysulfinylazetidinone derivatives.

In connection with penicillin-cephalosporin conversion, disulfides 1, readily accesible from natural penicillins by Kamiya's method,[2a)] are one of most actively investigated intermediates.[2)] Namely, the disulfides 1 can be converted by the action with bromine or $CuCl_2$ in CH_2Cl_2 to the corresponding 2β-halomethylpenicillins 2 (X = Br, Cl), which are a good precursor of useful cephalosporin antibiotics.[2)]

Recently, an alternative procedure of the S-S bond fission of 1 by the electrolysis in a $(CH_3)_4NBr$-$ClCH_2COOH$-aqueous CH_3CN (Pt electrodes) system has been reported.[3)] This electrolysis system provides 3β-bromocepham 3 (X = Br, 18-45%) along with a small amount of deacetoxycephalosporins 4 after

Scheme 1



isomerization of the primary products 2 (X = Br) on the chromatographic purification.[4] This prompted us to report our distinguishable results on the electrolytic S-S bond cleavage of the disulfides 1, leading to halopenicillins 2 (X = Br, Cl), halocephams 3 (X = Br, I), and/or 4-methoxysulfinylazetidinone 7, respectively.[5]

The electrolysis was carried out in an undivided cell fitted with two Pt electrodes (1.5 × 2 cm^2). A typical electrolysis procedure (entry 1 in the Table) is as follows: A solution of the disulfide 1a (R^1 = $PhCH_2$, R^2 = CH_3, 86 mg, 0.17 mmol) and $MgBr_2$ (85 mg, 0.19 mmol) in CH_3CN (6 ml), tetrahydrofuran (THF, 1.5 ml) and H_2O (0.3 ml) was electrolyzed at 10 mA/cm^2 at 23-25 °C. After passage of 4 F/mol of electricity (35 min), the usual workup followed by column chromatography (SiO_2, benzene/AcOEt: 5/1) yielded 2a (R^1 = $PhCH_2$, R^2 = CH_3, X = Br, 52%) and 3a (R^1 = $PhCH_2$, R^2 = CH_3, X = Br, 44%) along with bis(2-benzothiazolyl)disulfide (31 mg). Some of the results together with the electrolysis conditions are summarized in the Table.

Among various kinds of bromide salts, $MgBr_2$ was the most effective one for this purpose. Thus, use of alkaline metal salts, e.g., LiBr, NaBr, and KBr or HBr in place of $MgBr_2$ afforded a mixture of 2a and 3a in 73-46% yields (entries 2-5), while ammonium bromides are ineffective, affording only dimer 6 and/or decomposition products (entries 6 and 7).[6] In contrast to the reported results,[7] electrolysis of 1a with $MgCl_2$ in the same medium brought about the exclusive formation of the corresponding chloropenicillin 2b (R^1 = $PhCH_2$, R^2 = CH_3, X = Cl) (entry 8). However, iodide salts, e.g., MgI_2 and NaI are less effective, leading to a small amount of iodocepham 3c (R^1 = $PhCH_2$, R^2 = CH_3, X = I, < 20%) along with dimer 6 (26-41%)(entries 9 and 10). Interestingly, the electrolytic conversion of 1a to 2b could be achieved by using two-phase electrolysis system, comprising aqueous chloride salts and CH_2Cl_2 (entries 11 and 12). Similar attempts with bromide salts and iodide salts in the two-phase electrolysis system failed (entries 13 and 14).

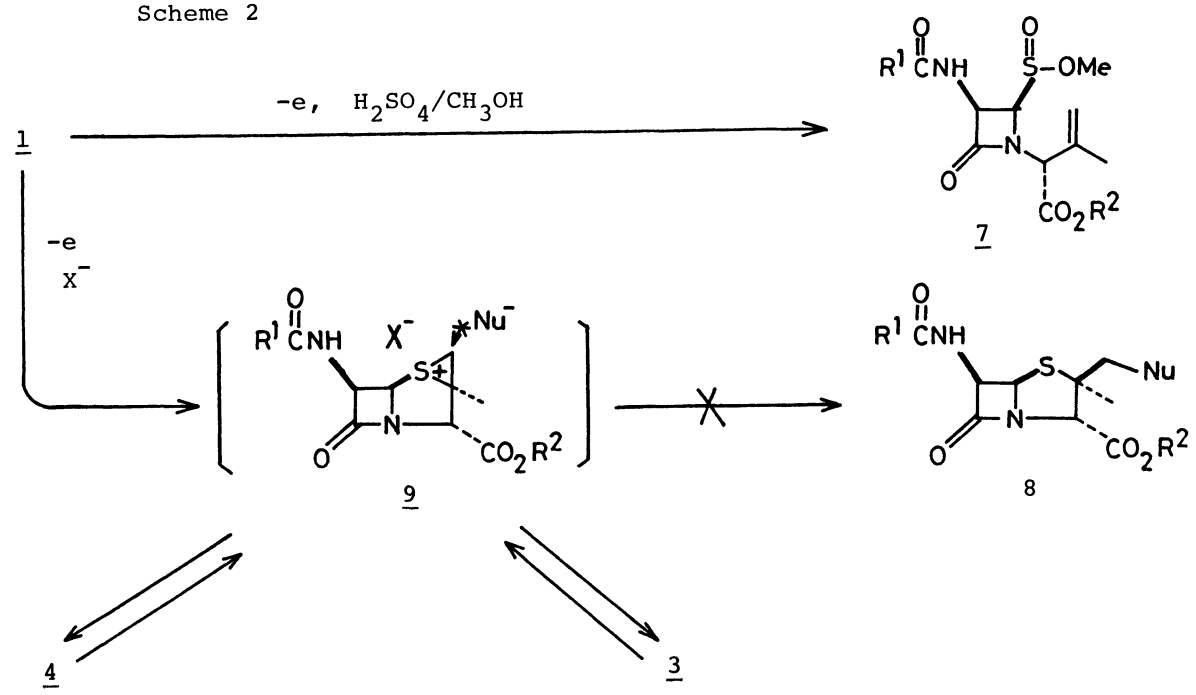
Apparently, the product ratio of halopenicillins 2 to halocepham 3 varied remarkably depending on the choice of halide salts as well as the electrolysis conditions. The ratio of 2a to 3a (X = Br) was also affected by the employed temperature as follows: temperature, 2a/3a (total yields): 23-25 °C, 54/46 (96%); 5-9 °C, 80/20 (100%); -3~-5 °C, 88/12 (90%). The results so far obtained suggest that in the initial stage of the electrolysis, kinetically favored halopenicillins 2 (X = Br, Cl, and I) are formed *via* episulfonium ion 9 (Scheme 2) by the action with the anodically generated X^+ or X_2 (X = Br, Cl, and I) in a similar fashion to the reported chemical conversion.[2a] Then, the isomerization of 2 (X = Br and I), having a good leaving group at the C-2' position, to 3 would take place in the electrolysis media and partly under the workup conditions. However, the chloropenicillin 2b (X = Cl) would be stable enough in the electrolysis media to be recovered intact. The transformation of 2a (X = Br) into 3a could be performed by standing in N,N-dimethylformamide (DMF) at room temperature overnight[2a] and subsequent chromatography on a Al_2O_3 column with benzene/AcOEt (1/1) afforded deacetoxycephalosporin 4 (R^1 = $PhCH_2$, R^2 = CH_3,

Table Electrolysis of Disulfide 1a (R^1 = $PhCH_2$, R^2 = CH_3) with Halide Salts[a)]

entry	halide salt[b)]	solvents[c)]	Products, yields %[d)]			
			2 + 3 (2/3)	5	6	1
1	$MgBr_2$	A	96 (54/46)	--	--	--
2	LiBr	A	73 (38/62)	--	--	18
3	NaBr	A	74 (35/65)	--	--	22
4	KBr	A	58 (50/50)	--	25	21
5	HBr	A	46 (65/31)	--	--	14
6	Et_4NBr	A	--	--	--	15
7	NH_4Br	A	--	--	52	32
8	$MgCl_2$	A	66 (100/0)	--	--	15
9	NaI	A	20 (0/100)	--	41	14
10	MgI_2	A	trace	--	26	68
11	NaCl	B	72 (100/0)	5	--	26
12	$MgCl_2$	B	65 (100/0)	--	--	30
13	NaBr	B	--	--	--	90
14	NaI	B	--	--	--	100

a) Carried out at 10 mA/cm^2, passing 4 F/mol of electricity, at 23-27 °C. b) A stoichiometric amount of halide salts was added. c) A: $CH_3CN/THF/H_2O$ (6/1.5/0.3); B: CH_2Cl_2/H_2O (5/3); d) Isolated yields after column chromatography (SiO_2, benzene/AcOEt: 5/1).

Scheme 2



95%).

With regard to the isomerization (2→9→3) in the aqueous medium, it is notable that the solvolyzed products 8 (Nu = OH and $NHCOCH_3$) could not be detected, which are expected to be generated by the attack of the solvents to 9.[2b] Several attempts to trap the intermediate 9 by using aqueous or protic solvents, e.g., aqueous acetone, aqueous THF, aqueous DMF, and methanol, failed, but the electrolysis of 1a (250 mg, 0.5 mmol) in methanol (50 ml) containing conc. H_2SO_4 (0.4 ml) afforded 4-methoxysulfinylazetidinone 7 (R^1 = $PhCH_2$, R^2 = CH_3, 53%), which is a new class of intermediate for β-lactam antibiotic synthesis.[8]

References

1) Penicillin-Cephalosporin Conversion V.

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3) (a) A. Balsamo, P. Benedini, I. Giorgi, B. Macchia, and F. Macchia, Tetrahedron Lett., 23, 2991 (1982); (b) Details on the S-S bond fission by the halide salts promoted electrolysis have been already discussed: S. Torii, H. Tanaka, and M. Ukida, J. Org. Chem., 44, 1554 (1979); S. Torii, N. Sayo, and H. Tanaka, Tetrahedron Lett., 4471 (1979).

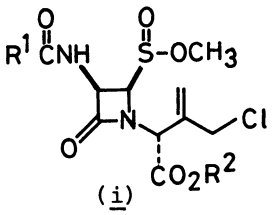
4) Although they have experienced some difficulties on the isolation of the intermediates 2, we could obtained 2 (R^1 = $PhCH_2$, R^2 = CH_3, X = Br and Cl) smoothly after column chromatography on SiO_2. They have confirmed their intermediates 2 by the transformation into the corresponding S-oxides (see ref. 3a).

5) The outline of this work has been presented by T. S. at the 45th annual meeting of Chem. Soc. Jpn. in Tokyo, on April 4. 1982: The Abstracts of Papers, Vol. 2, p. 1033.

6) Similar results have been obtained in the electrolysis of 1 in a $(CH_3)_4NBr$-aqueous CH_3CN system (see ref. 3a).

7) The electrolytic conversion of 1 into chloropenicillins 2 (X = Cl) has been attempted by using chloride salts, but has not yet been realized (see ref. 3a).

8) The electrolytic ene-type chlorination of 7 proceeded smoothly to give a potent intermediate (i). Further transformation of (i) into useful β-lactam antibiotics is under progress.



(i)

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