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Electrooxidative Cyclization of 4-Dithioazetidinones (Kamiya's Disulfides) A Facile Access to 2-(Substituted methyl)penicillanates

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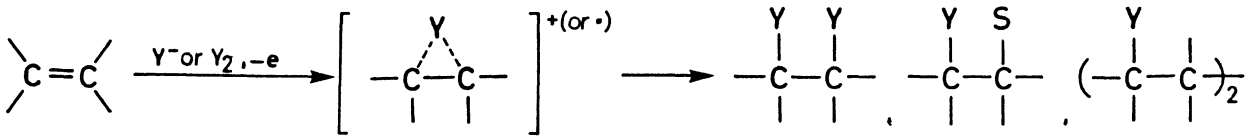
A straightforward access to penicillanates bearing SCN and SeCN groups at the 2β-methyl group was performed by electrolysis of 4-dithioazetidinones in a two-phase system (aqueous and organic phases) in the presence of KSCN and KSeCN, respectively, while a mixture of 2β-azidomethyl derivative and its 2α-isomer (6/4) was obtained by a similar electrolysis with NaN_3.

Since the discovery of β-lactamase inhibitory properties of clavulanic acid,[1] a variety of inhibitors has appeared in the literature. Among them, penicillanic acid dioxide **4** (Y = H, Sulbactam)[2a] and its homologues bearing substituents (Y), e.g., Cl,[2b] N_3,[2c] SCN,[2d] triazolyl,[2e] and tetrazolylthio,[2d] at the 2β-methyl groups have attracted much attention as a promising β-lactamase inhibitor. The introduction of the proper substituent (Y) to the 2β-methyl group of **4** has generally relied on replacement of the chlorine atom of chloromethylpenams **3** (Y = Cl), derived from dithioazetidinones **1** by the action of Cl_2[3] or $CuCl_2$,[2c] or by electrolytic chlorination.[4]

Recently, the electrochemical olefin addition of Y^- (or Y_2), e.g., SCN^-, N_3^-, diphenyldiselenide, and diphenyldisulfide, has been reported, in which, electrogenerated electrophilic species Y^+ (or $Y^\cdot$) would attack olefins to generate an intermediary onium ion (or radical) (Scheme 1).[5] This prompted us to investigate the possibility of the direct transformation of **1** into 2β-(substituted methyl)penam **3** through onium (or radical) intermediates **2** as expected to be formed in similar electrolysis media (Scheme 2). Herein, we describe a straightforward access to 2-(substituted methyl)penicillanate **3** (Y = SCN, SeCN, N_3) by a simple electrolysis procedure.

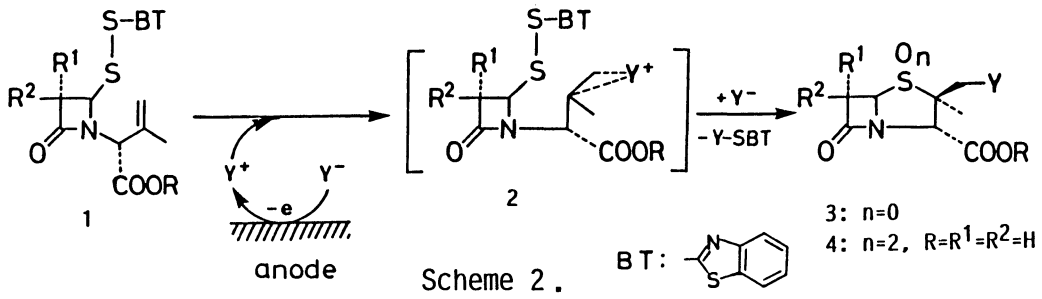
The electrolysis was carried out in an undivided cell fitted with two Pt



Y^-: SCN^-, N_3^-
Y_2: PhSe-SePh, PhS-SPh

S: OH, OCH_3, OAc, NHAc

Scheme 1.

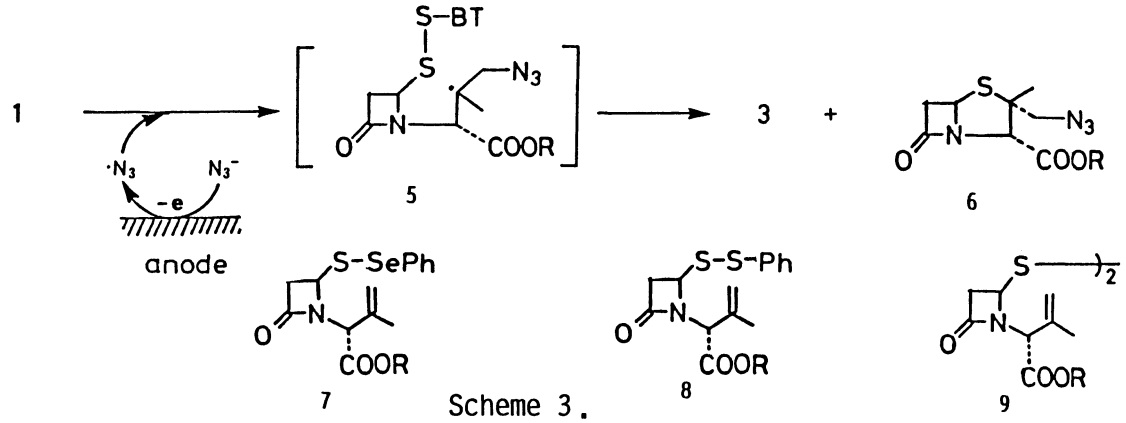


Scheme 2.

electrodes (1.5 x 2 cm^2). Some of the results are summarized in Table 1. A typical electrolysis procedure (entry 1 in Table 1) is as follows: A mixture of the 4-dithioazetidinone **1** (R = PNB, R^1 = R^2 = H, 0.5 mmol) and KSCN (3 mmol) in CH_2Cl_2 (4 ml), H_2O (4 ml), and 0.2N H_2SO_4 (0.5 ml) was electrolyzed at 10 mA/cm^2 at room temperature. After most of **1** was consumed (12 h), the usual workup followed by column chromatography (SiO_2, benzene-AcOEt) afforded **3** (Y = SCN, 97%) along with bis(2-benzothiazolyl)disulfide (BTS-SBT, 99%). Notably, two-phase electrolysis system consisting of aqueous and CH_2Cl_2 phases is indispensable for the present purpose; otherwise (entries 4 and 5), the decomposition of **1** mainly occurs to give a complex mixture. The presence of acids, e.g., H_2SO_4 and AcOH, in the electrolysis media is effective for improving the current efficiency in some extent (entries 1-3).

The two-phase electrolysis procedure can be successfully applied to various 4-dithioazetidinones **1** to give the 2β-thiocyanatomethylpenams **3** (entries 6-9). Furthermore, the electrolytic selenocyanation is achieved by slight modification of the electrolysis media. Thus, the electrolysis of **1** (R = PNB, R^1 = R^2 = H) with KSeCN in a benzene-acetonitrile-H_2O-AcOH system afforded 2β-selenocyanatomethylpenam **3** (Y = SeCN) in 90% yield (entry 10). On the other hand, electrolysis of **1** with NaN_3 in the homogeneous solution took place more efficiently than that in two-phase system (entries 13 and 14), affording a mixture of the corresponding 2β-azidomethylpenam **3** and the 2α-isomer **6** (6/4).[6)]

Although reaction mechanism is still unclear, it is likely that formation of Y^+ (or Y_2) by two electron oxidation of Y^- is followed by the electrophilic attack on the terminal olefin of **1** affording **2** and subsequent cyclization of **2** leads to the final products **3** (Y = SCN or SeCN). The formation of a mixture of 2β- and 2α-azidomethylpenam **3** ($Y = N_3$) and **6** would involve epimerization of radical intermediate **5** generated in the analogous way (Scheme 3) before the



Scheme 3.

Table 1. Electrosynthesis of 2β-(substituted methyl)penams **3**

Entry	Dithioazetidinone **1**			Y^-	Conditions		Products **3**	
	R^1	R^2	R[b]		Solvent-System (ml)	F/mol[c]	Yield/%[d]	
1	H	H	PNB	KSCN	CH_2Cl_2-H_2O-0.2N H_2SO_4 (4/4/0.5)	14	97	
2	H	H	PNB	KSCN	CH_2Cl_2-H_2O (4/4)	27	98	
3	H	H	PNB	KSCN	CH_2Cl_2-H_2O-AcOH (4/4/1)	20	93	
4	H	H	PNB	KSCN	MeCN-H_2O (5/2)	6	decomp.	
5	H	H	PNB	KSCN	DMF-AcOH (5/2)	15	decomp.	
6	H	H	PMB	KSCN	CH_2Cl_2-H_2O-0.2N H_2SO_4 (4/4/0.5)	14	98	
7	H	H	Bh	KSCN	CH_2Cl_2-H_2O-0.2N H_2SO_4 (4/4/0.5)	12	89	
8	Br	H	PNB	KSCN	CH_2Cl_2-H_2O-0.2N H_2SO_4 (4/4/0.5)	14	54	(44)[e]
9	H	PhCH2CONH	Bn	KSCN	CH_2Cl_2-H_2O-0.2N H_2SO_4 (4/4/0.5)	27	80	
10	H	H	PNB	KSeCN	C_6H_6-MeCN-H_2O-AcOH (6/1/3/1)	22	90	
11	H	H	PNB	KSeCN	CH_2Cl_2-H_2O (6/1)	21	20	(77)[e]
12	H	H	PNB	KSeCN	CH_2Cl_2-H_2O-AcOH (3/2/1)	21	75	
13	H	H	PNB	NaN_3	DMF-AcOH (4/5)	4	22[f]	(56)[e]
14	H	H	PNB	NaN_3	CH_2Cl_2-H_2O-AcOH (7/2/1)	4	5[f]	
15	H	H	PMB	$(PhSe)_2$	MeCN-0.2N H_2SO_4 (8/0.5)	4	--	
16	H	H	PMB	$(PhS)_2$	MeCN-0.2N H_2SO_4 (8/0.5)	4	--	

a) Electrolysis was carried out in an undivided cell fitted with two platinum electrodes (1.5 x 2 cm^2) at room temperature except for entry 13 (at 0 °C).
b) PNB: p-nitrobenzyl, PMB: p-methoxybenzyl, Bh: benzhydryl, Bn: benzyl.
c) Unless otherwise noted, constant current (entries 1-14: 10 mA/cm^2, entries 15 and 16: 3.3 mA/cm^2) was supplied until most of dithioazetidinones **1** was consumed.
d) Isolated yields. e) Recovered **1**. f) A mixture of **3** (Y = N_3) and **6** (6/4).

cyclization to thiazolidine ring formation (**5**→**3** and **6**). A similar epimerization to that of radical intermediates **5** has been observed in either photolysis of 4-dithioazetidinone **1** (R = CH_3, R^1 = H, R^2 = $PhCH_2CONH$)[7] or in biomimetic synthesis of penicillin.[8]

Next, electrolysis of **1** with diphenyldiselenide or diphenyldisulfide was carried out in a similar manner (entries 15 and 16). However, no appreciable amounts of cyclized products **3** were observed; former affording phenylselenothioazetidinone **7** (74%) and latter affording a mixture of phenyldithioazetidinone **8** (20%) and dimer **9** (71%). Presumably, electrophilic species ($PhSe^+$, $PhSe^{+\cdot}$-SePh, PhS^+, $PhS^{+\cdot}$-SPh) generated in the electrolysis media would attack the disulfide moiety of **1** preferentially rather than the olefin.

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