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$MgBr_2$-PROMOTED ELECTROSYNTHESIS OF SULFENIMINES (THIOOXIMES) FROM α-AMINOALKANOATES AND DIARYL/DIALKYL DISULFIDES IN A CH_2Cl_2-H_2O TWO-PHASE SYSTEM.[1] A STRAIGHTFORWARD PREPARATION OF C(6)/C(7)-SULFENIMINE DERIVATIVES OF PENICILLIN AND CEPHALOSPORIN

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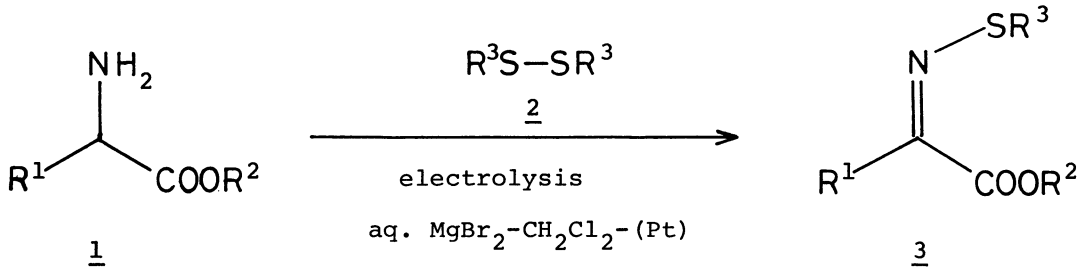
Direct transformation of α-aminoalkanoates and diaryl or dialkyl disulfides to the corresponding sulfenimines by electrolysis in a CH_2Cl_2-H_2O-$MgBr_2$-(Pt electrodes) system and its application to the sulfenylation of C(6)/C(7)-amino groups of penicillin and cephalosporin are described.

Sulfenimine (Thiooxime) is a valuable synthetic intermediate as a secondary imine equivalent.[2] Sulfenimines have been prepared by condensation of primary sulfenamides ($RSNH_2$) with ketones or aldehydes,[3] sulfenylation of amines with excess sulfenyl chlorides (3 equiv.),[2b, c] oxidation of sulfenamides with MnO_2[2c] or sulfenyl chlorides,[2b] and others.[4] However, direct transformation of readily available disulfides and amines into sulfenimines has not yet been realized.

In the course of our investigation on the halide-promoted electrosynthesis of hetero-hetero atom bonds,[1] we found that electrolytic cross-coupling of α-aminoalkanoates 1 and disulfides 2 into sulfenimines 3 took place smoothly in a CH_2Cl_2-H_2O-$MgBr_2$-(Pt electrodes) system, which involves both anodic and cathodic reactions, so-called "paired reaction". Such electrolytic paired reaction could be successfully applied to the sulfenylation of C(6)-aminopenicillin 9p and C(7)-aminocephalosporin 9c into the corresponding C(6)/C(7)-sulfenamide and/or C(6)/C(7)-sulfenimine derivatives 10 and 11, respectively.

The electrolysis was carried out in a beaker-type undivided cell, fitted with two Pt electrodes (1.5 × 2 cm^2). A typical electrolysis procedure (entry 1 in Table 1) is as follows. An aqueous $MgBr_2$ solution (0.3 mmol/4 ml) and a



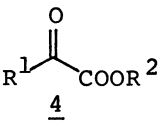
1 3

CH_2Cl_2 solution (3 ml) of α-aminoalkanoate 1a (R^1 = i-Bu; R^2 = Et, 0.6 mmol) and disulfide 2a (R^3 = Ph, 0.6 mmol) were charged into the cell. Under vigorous stirring at room temperature, regulated dc-power (10 mA/cm^2) was supplied until most starting material 1a was consumed (2.5 F/mol of electricity passed). After usual workup and short-path column chromatography (SiO_2, hexane/AcOEt:10/1) sulfenimine 3a (R^1 = i-Bu; R^2 = Et; R^3 = Ph) was obtained in 83% yield. The results of the electro-coupling of α-aminoalkanoates 1 with diaryl and dialkyl disulfides 2 are summarized in Table 1.

The two-phase electrolysis system comprising aqueous and organic (CH_2Cl_2) phases was effective for the successful transformation of 1 and 2 into 3. In contrast, a combination of water and hydrophylic organic solvent, e.g., H_2O-THF, H_2O-dioxane, and H_2O-CH_3CN, brought about crucial formation of a complex mixture of decomposition products involving α-keto esters 4 (15-20%).

Notably, the presence of $MgBr_2$ in the electrolysis media is indispensable. The yield of desired 3a strikingly depends on the choice of halide ion: $MgBr_2$ (93%); MgI_2 (57%); $MgCl_2$ (27%). The effects of the counter ion of Br^- are also remarkable: NH_4Br (41%); NaBr (25%); LiBr (24%). These facts suggest that both Mg^{2+} and Br^- play significant roles in the S-N coupling of 1 and 2 into 3. Although the mechanism is still uncertain, the transformation of 1 and 2 into 3 can be explained by assuming the following set of paired reaction (Eqs. 1-7).

As shown in Eq. 3, it is likely that the electro-generated Br_2 (Eq. 1) favorably attacks amine 1 (→5) rather than disulfide 2 (→7). In fact, electrolysis of 1a in the aqueous $MgBr_2$-CH_2Cl_2 two-phase system (3 F/mol) afforded the corresponding α-keto ester 4 (68%), presumably via 5, whereas disulfides 2 were recovered (75-90%) under the same electrolysis conditions. Subsequently, the N-bromoamine 5 would react with the disulfide 2 to give sulfenamide 6 and sulfenyl bromide 7 (Eq. 4), latter of which would, in turn, react with the additional amine

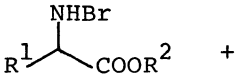


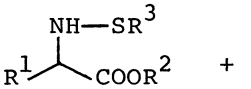
Aqueous Phase

Anode: $2\ Br^- \xrightarrow{-2e^-} Br_2$ (1)

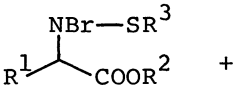
Cathode: $Mg^{2+} + 2\ H_2O \xrightarrow{+2e^-} Mg(OH)_2 + H_2$ (2)

Organic Phase

$1 + Br_2 + OH^- \longrightarrow$  $+ Br^- + H_2O$ (3)

$5 + 2 \longrightarrow$  $+ R^3S-Br$ (4)

$1 + 7 + OH^- \longrightarrow 6 + Br^- + H_2O$ (5)

$6 + Br_2 + OH^- \longrightarrow$  $+ Br^- + H_2O$ (6)

$8 + OH^- \longrightarrow 3 + Br^- + H_2O$ (7)

Table 1. Direct Electrosynthesis of Sulfenimine from α-Aminoalkanoate[a)]

Entry	α-Aminoalkanoate 1		Disulfide 2	Electricity[b)]	Product 3
	R^1	R^2	R^3	F/mol	Yield / %[b,c)]
1	$CH(CH_3)_2$	C_2H_5	Ph	2.5	83
2	$CH(CH_3)_2$	C_2H_5	Bu^t	3	60
3	$CH(CH_3)_2$	C_2H_5	BT[d)]	2.5	55
4	Ph	CH_3	Ph	3	92
5	Ph	C_2H_5	Ph	3	93
6	Ph	C_2H_5	p-$NO_2C_6H_4$	3	88
7	Ph	C_2H_5	Bu	3	75
8	Ph	C_2H_5	Bu^t	3	69
9	$(CH_2)_2COOC_2H_5$	C_2H_5	Ph	3.2	80
10	$CH_2COOC_2H_5$	C_2H_5	Ph	3.5	79

a) Carried out in a $MgBr_2$-H_2O-CH_2Cl_2-(Pt electrodes) system at 10 mA/cm^2 at room temperature. b) Based on α-aminoalkanoate 1. c) Isolated yields after column chromatography (SiO_2, hexane/AcOEt: 10/1). d) 2-Benzothiazolyl.

Table 2. Electrolytic Conversion of Sulfenamide into Sulfenimine[a)]

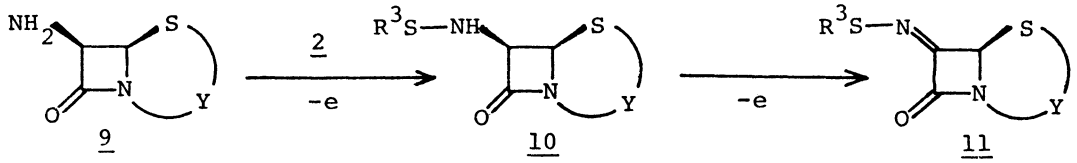
Entry	Sulfenamide 6[b)]		Electricity	Product 3
	R^1	R^3	F/mol	Yield / %[c)]
1	$CH(CH_3)_2$	Ph	2.2	83
2	$CH(CH_3)_2$	BT[d)]	2.5	70
3	Ph	Ph	2.5	96
4	$(CH_2)_2COOC_2H_5$	Ph	2	81
5	$CH_2COOC_2H_5$	Ph	2	83

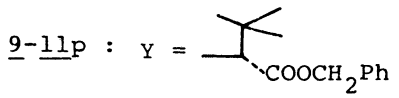
a) Unless otherwise noted, the electrolysis was carried out in a same manner as described above. b) $R^2 = C_2H_5$. c) Isolated yields after column chromatography (SiO_2, hexane/AcOEt: 10/1). d) 2-Benzothiazolyl.

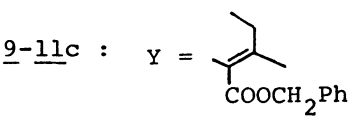
1, yielding 6 (Eq. 5). The intermediary sulfenamide 6 would be submitted to further oxidation, affording 3 (Eqs. 6 and 7). The transformation of 6 to 3 could be actually confirmed by the electrolysis of 6 in the same electrolysis media (see Table 2). In the course of the reaction, electro-generated base, $Mg(OH)_2$, (Eq. 2) would promote the proton-abstraction steps (Eqs. 3, 5, 6, and 7).

Next, we examined sulfenylation[2b,c] of C(6)/C(7)-amino groups of penicillin 9p and cephalosporin 9c in a slightly modified electrolysis system. Thus, electrolysis of 9p and disulfide 2 (R^3 = Ph) in a CH_2Cl_2-MeOH-H_2O (10/2.5/10)-$MgBr_2$-(Pt) system (4 F/mol) afforded 72% yield of sulfenimine 11p (R^3 = Ph). In a similar manner, sulfenimines 11p (R^3 = BT, 72%, 8 F/mol) and 11c (R^3 = Ph, 60%, 6 F/mol) were obtained. Interestingly, the intermediary sulfenamide 10p (R^3 = BT) was isolated in 87% yield by interrupting the electrolysis after passage of 3 F/mol of electricity. Conversion of 10p to 11p could be performed under similar electrolysis conditions in 71% yield.

Details on the electro-sulfenylation of 9 as well as further transformation of 11 into useful β-lactam compounds[5] will be reported in due course.







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