Table 2. Formation of *p*-Toluenesulfonyl Chloride (**3b**) from *p*-Toluenesulfonamide (**1b**) and Thionyl Chloride in Various Reaction Conditions

Entry	$SOCl_2$ (equiv)	Pyridine (equiv)	Temp	Time (hrs)	Yield[a] of **3b** (%)
1	3	10 mol%	reflux	9	55
2	3	2	reflux	9	59
3	3	2	RT	42	–
4	3	–[b]	reflux	9	–
5[c]	3	2	reflux	9	77
6[d]	3	2	reflux	9	49
7[e]	3	2	reflux	9	87
8	47	–	reflux	24	52
9	2	2	reflux	9	53
10	1	10 mol%	reflux	9	trace
11	1	2	reflux	9	trace
12	1	2	RT	24	–
13	1	–	reflux	9	–
14[c,f]	1	–	reflux	9	47

[a] Isolated yied. [b] Denotes absence. [c] In THF. [d] In hexane. [e] In 1,4-dioxane. [f] Starting material is N-sulfinyl *p*-toluenesulfonamide.

and benzoyl chloride (~30%) derivatives. Other compounds such as toluidines, *o*-anisidine, *m*-nitroaniline, and 2,4-dinitroaniline gave only the corresponding N-sulfinyl compounds. These results indicate that only the substrates having carbonyl- or sulfonyl group adjacent to -N=S=O, react with thionyl chloride. Therefore, carbonyl group of the benzamides and the sulfonyl group of arenesulfonamides seem to exert influences to make the sulfur in -N=S=O group more electrophilic enough to be able to react with thionyl chloride. In conclusion, this method can be utilized to deaminatively chlorinate the arenesulfonamide to give arenesulfonyl chloride.

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The Electrochemical Activation of Amino Acid 4-(Methylthio)phenyl Ester and Its Application in Peptide Synthesis

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The 4-(methylthio)phenyl (MTP) group has been utilized as a carboxyl protecting group in peptide synthesis, and revealed several advantages.[2] Thus, the MTP group can serve as a safety-catch type protecting group during peptide coupling reactions, and later the resulting peptide fragment can be oxidized by common oxidizing agents to sulfone ester, which is an active ester to be coupled with other N-free peptide fragments to form a new peptide bond.

In our previous reports, we have reported that the charge transfer (CT) interaction between Kaiser's oxime resin[3] and the MTP group accelerated the coupling reaction between the resin bound N-protected amino acid or peptide and the amino acid MTP ester, yielding the N-protected peptide MTP ester.[4] The released peptide fragment was oxidized to 4-(methylsulfonyl)phenyl (MSO_2P) ester and used in cyclization

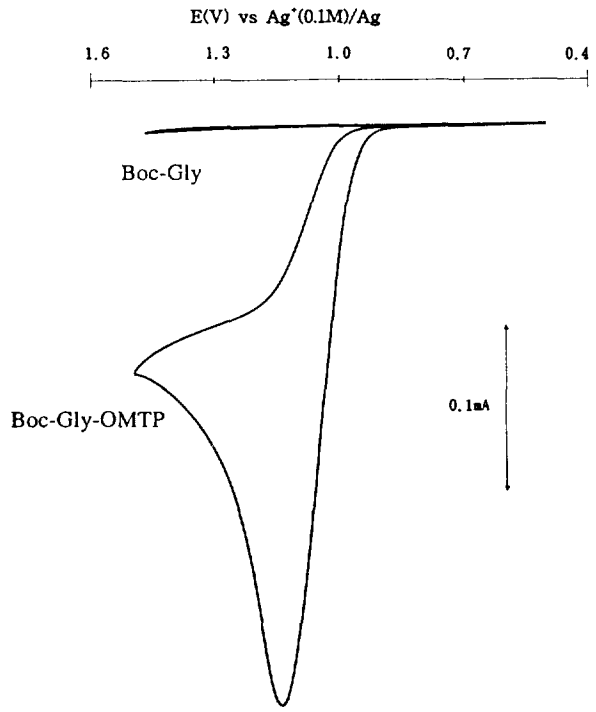


Figure 1. CV of Boc-Gly-OMTP and Boc-Gly.

Table 1. CV Peak Potentials of Various MTP Esters[a]

	Peak Potential[b] (Volt)
Boc-Gly-OMTP	1.12
Boc-Leu-OMTP	1.15
Boc-Phe-OMTP	1.17
Boc-Ala-OMTP	1.13
Boc-Met-OMTP	1.28
Boc-Gly	none
Boc-Met	1.45
Ac-OMTP	1.12

[a] Condition: 5 mM of Boc-AA-OMTP in acetonitrile with 0.1 M of $LiClO_4$ as supporting electrolyte. [b] Potential *vs.* Ag^+ (0.1 M)/Ag.

reaction after removing N-protected group.[5] As the oxidizing agent, *m*-chloroperbenzoic acid (*m*CPBA) has been used. But, excessive chemicals were needed for the complete oxidation to a sulfone and some tedious steps were needed to eliminate the remaining reagents and by-products. In these aspects, electrochemical oxidation reactions might have some merits; clean reactions with high selectivity, easy controllability, and no by-products.

Recently, Deleru-Matos *et al.*[6] have reported that the sulfur containing C-terminal protecting group, 2-(4-nitrophenylthio) ethyl group, can be electrooxidized to a sulfone with moderate yields. But, they have focused only on the removal of the protecting group after the oxidation, not on the peptide coupling reaction. Comparing with this, the electrochemical oxidation of MTP ester should have another advantage. The oxidized product can not only be cleaved by mild base yielding C-free peptide fragment but also be directly coupled by another amino acid or peptide fragments. Therefore, we have tried electrochemical oxidation of several amino acid MTP ester derivatives to the corresponding sulfone esters and proved its effectiveness on peptide synthesis. We now wish to report the preliminary results from this work.

Several Boc (or Cbz)-amino acid MTP esters were prepared according to the written procedure[2], and their cyclic voltammograms (CV) were measured. The results have demonstrated that Boc-Gly-OMTP had an oxidation peak at 1.12 V *vs.* Ag/Ag^+ (0.1 M), while Boc-Gly had not. (Figure 1) The peak potentials of other amino acid MTP esters are summarized in Table 1.

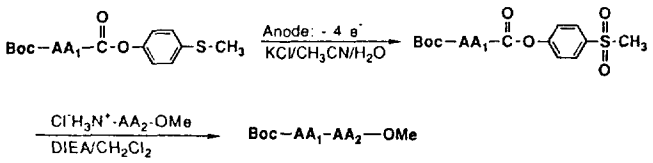
From this we can confirm that the anodic currents are due to the oxidation of phenyl methyl sulfide in MTP esters, and it occurs even at lower potential than alkyl sulfide of Boc-Met (1.45 V), even though it is not clear yet whether the products are sulfoxides or sulfones.

To obtain the oxidized product in large amount, a controlled potential electrolysis of Boc-Gly-OMTP was performed at 1.10 V in a two compartment cell. During the electrolysis, the reaction products were examined by HPLC.[7]

After 3 hours, Boc-Gly-OMTP was completely converted to a new compound. Comparing with the authentic samples, the products proved to be Boc-Gly-4-(methylsulfoxy)phenyl (MSOP) esters, which needed further oxidation for peptide coupling reaction with another N-free amino acid. If the electrolysis was performed at a higher voltage than 1.6 V, some by-products would begin to form. Therefore, direct electrolysis does not benefit the conversion of MTP ester to the corresponding 4-(methylsulfonyl)phenyl (MSO_2P) ester.

Generally, mediators have been used in order to reduce the overpotential or improve the selectivity for specific reactions.[8] Therefore, we used KCl and KBr as mediators in order to get the sulfone ester. Typical reaction procedures are as follows. 0.2 g of Boc-Phe-OMTP in 30 m*l* acetonitrile was combined with 20 m*l* of 0.1 M KBr aqueous solution which was acidified to pH 5-6 with few drops of acetic acid, stirred vigorously, and then constant current (6.25 mA/cm^2) was applied from Pt electrodes to the cell. When the current was applied, the solution turned brown gradually, and we could observe that bromine was generated at the anode and hydrogen at the cathode. During the reaction, the aliquots of the reaction mixture were examined by HPLC. The product analyses have revealed that Boc-Phe-OMTP was oxidized to a sulfoxide/sulfone mixture, and the oxidation reaction did not proceed any further. But when KCl was used as a mediator, the same condition has led to the complete oxidation of Boc-Phe-OMTP into a sulfone, Boc-Phe-$OMSO_2P$ in 75 minutes (5.6 F/mole; isolated yield, 61%).

The similar anodic oxidation of diaryl sulfide in halide media has been reported previously.[9] More examples of reactions that involve electrogenerated halogen can be found in the literature.[10] The observation that the two halides show the different results can be explained by the different activities of the several halogen species which are generated at different equilibria when the electrogenerated Br_2 and Cl_2 are dissolved in water. The main species which are generated by each halogen depend on their concentrations and pH. Under the reaction conditions when Br_2 and Cl_2 are generated at the anode (pH 5-6), the main halogen form from Cl_2 is HOCl[11] and the one from Br_2 is Br_2(aq.)[12] The oxidation of Boc-Phe-OMTP may be carried out by these species. In



Scheme 1.

Table 2. The Results of Dipeptide Synthesis

Dipeptide	Overall Yield (%)	MP (℃)	Lit mp. (℃)	Ref
Boc-Phe-Phe-OMe	53	114-115	114-115	15[a]
Boc-Phe-Gly-OMe	48	90	91	15[b]
Boc-Phe-Val-OMe	50	119-120	120-122	15[c]
Boc-Ala-Gly-OMe	41	oil	oil	15[d]
Boc-Leu-Gly-OMe	52	132-133	131-132	15[e]
Boc-Leu-Val-OMe	40	146-147	143-147	15[f]
Cbz-Phe-Leu-OMe	55	109-110	109-109.5	15[g]
Boc-Gly-Gly-OMe	41	oil	–	

comparison to these two electrogenerated halogen species, HOCl has a much stronger oxidizing ability (E_o = 1.484 V) than Br_2(aq) (E_o = 1.066 V).[13] Moreover, it can act as a direct oxygen source.[14] So it becomes clear that the electrogenerated HOCl can oxidize Boc-Phe-OMTP more effectively. With these results we have prepared various dipeptides from Boc (or Cbz)-amino acid MTP esters (Scheme 1).

After the same electrochemical oxidation, the crude products were treated with aq. $NaHSO_3$ to quench any remaining active halogen species, and saturated with KCl. The organic layer was separated, evaporated to an oily residue, which was crystallized in acetonitrile/water. Then, 3 equiv. of amino acid methyl esters and 3 equiv. of diisopropylethylamine (DIEA) were added to the MSO_2P ester in methylene chloride. After stirring overnight at room temperature and the usual work-up gave dipeptides in 40-55% overall yields. The results are summarized in Table 2.

In conclusion, the direct electrooxidation of amino acid MTP ester has only yielded the corresponding sulfoxy ester. But when KCl was used as a mediator, the electrochemical oxidation of MTP ester gave the corresponding sulfonyl ester. Then, the amino acid MSO_2P esters were easily coupled with another amino acid derivatives, yielding dipeptides effectively. We are now focusing on the optimization of the electrooxidation conditions to improve the yields.

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Temperature-Dependence of Mouse Brain Membrane-Bound Acetylcholinesterase Systems: Manifestation of $\Delta H^{\neq}$-$\Delta S^{\neq}$ Compensation

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Acetylcholinesterase (AChE, EC 3.1.1.7) from a variety of sources has been found in association with membranes and in many cases tightly embedded in the membrane[1-3]. However, the exact relationships of the enzyme kinetic properties with this association and moreover the effect of temperature-dependent phase transition of the membrane-lipid on the