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Adsorption effects on the selective electrofluorination of α-(phenylthio)acetamides and α-(phenylthio)acetates in $Et_3N{\cdot}3HF/CH_3CN$

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Abstract

Cyclic voltammetric behaviour of α-(phenylthio)acetamides and α-(phenylthio)acetates were compared in CH_3CN/tetrabutylammonium perchlorate (TBAP) and $CH_3CN/Et_3N{\cdot}3HF$ to assess the influence of fluoride ion on the oxidative pathway. These studies support the Pummerer mechanistic pathway involving an initial attack at sulfur in selective electrofluorination (SEF). A linear correlation between the peak current values in cyclic voltammetry and overall synthetic yield in preparative electrolysis was obtained suggesting the importance of weak blocking or a reactive adsorption effect on the overall synthetic processes. Other factors influencing the adsorption and insulation of electrode surfaces during the SEF are also discussed. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Selective electrofluorination; Adsorption effects; α-(phenylthio)acetamides; α-(phenylthio)acetates

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1. Introduction

In contrast to earlier attempts towards nuclear fluorination [1], current efforts were mainly oriented towards side chain fluorination [2,3]. Among the active methylene groups, those containing $–S–CH_2–Z$ were found to undergo very facile selective electrofluorination (SEF) where Z is an electron withdrawing substituent [4–6] or a nitrogen heterocyclic ring [7,8]. The selective electrochemical fluorination (SEF) of ethyl α-(phenylthio)acetate ($PhSCH_2COOEt$) was studied as a model compound in greater detail using a flow cell and different anode materials [9] and T. Fuchigami has recently reviewed this [10]. The effect of substituents on the overall efficiency of SEF has also been recently evaluated [11,12].

The mechanism of SEF was initially assumed to be of an ECEC type involving electron transfer, proton release, electron transfer and nucleophilic fluoride attack; in this sequence.

However, Fuchigami and his co-workers, have proposed a Pummerer mechanism involving initial oxidation at sulfur to explain the facile nature of this class of compounds [6] (Scheme 1).

The difference in the efficiencies of anodic fluorination and methoxylation under identical conditions was cited as the evidence for this mechanism [6]. However, it would be worthwhile to look for further evidence in support of this pathway from voltammetric [13,14] as well as preparative electrolytic studies. This is the objective of the present work.

2. Experimental

The purity of the samples was checked by HPLC (Shimadzau LC 8-A) with a Shim-pack (4.0 mm × 25 cm) ODS column and 100% methanol as eluent. FT IR spectra of the starting materials were taken with a Perkin-Elmer 783 spectrometer. ^1H NMR spectra were taken with a Brucker NMR spectrometer at 90 MHz with tetramethylsilane as internal standard and $CDCl_3$ as solvent and ^{19}F NMR spectra with a Brucker WP 80 CY spectrometer at 75.4 MHz with $CFCl_3$ as standard and $CDCl_3$ as solvent. Positive shifts were designated as negative.

Acetonitrile (CH_3CN, HPLC grade) was obtained from SRL. The electrolyte $Et_3N{\cdot}3HF$ was prepared by mixing Et_3N and anhydrous HF (AHF) at low temperature and evaluating the HF content by titration. Tetrabutylammonium perchlorate (TBAP) was dried in a vaccum dessicator and used. A series of substituted α-(phenylthio)acetamides $PhSCH_2CONHR'$ where

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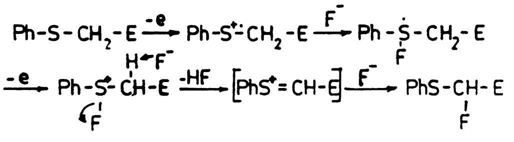


Scheme 1. Pummerer Mechanism

$$R' = C_6H_4 - Cl - p\ (\mathbf{3}a)$$

$$R' = H\ (\mathbf{5}a)$$

$$R' = C_6H_4 - NO_2 - p\ (\mathbf{6}a)$$

$$R' = C_6H_5\ (\mathbf{7}a)$$

and α-(phenylthio)acetates $PhSCH_2COOR''$ where

$$R'' = CH_3\ (\mathbf{1}a)$$

$$R'' = C_6H_4 - Cl - p\ (\mathbf{2}a)$$

$$R'' = C_6H_4 - NO_2 - p\ (\mathbf{4}a)$$

$$R'' = C_6H_5\ (\mathbf{8}a)$$

were prepared and characterised by measuring the m.p. or b.p., IR and NMR [15].

Cyclic voltammetry was performed as previously described [16]. Preparative electrolysis was carried out at Pt anode and cathode (area 9 cm^2) at 25°C ± 1°C under a dry N_2 atmosphere. The electrolyte 0.3 M $Et_3N{\cdot}3HF/CH_3CN$ was placed in the undivided cell and pre-electrolysed at 3.0 V until the current dropped to a constant value of10 mA. The 5 mmol of compound was added and electrolysed with the polarities of the electrode being reversed at interval of 10 s.

After passage of charge for (2 + 0.4F/mol) reaction, mono as well as difluoro products were obtained.

$$\underset{(\mathbf{1a-8a})}{PhSCH_2R} \xrightarrow{Et_3N\cdot 3HF/CH_3CN} \underset{(\mathbf{1b-8b})}{PhSCHFR} + \underset{(\mathbf{1c-8c})}{PhSCF_2R}$$

The solution was neutralised with aqueous ammonia and acetonitrile was evaporated. The liquid content was poured into 100 ml of water and extracted with ether. The ether layer was washed with brine solution (200 ml), the ether phase was dried over anhydrous $MgSO_4$. HPLC was mainly used to find the product distribution after each experiment. Under optimum conditions, prolonged preparative electrolysis was carried out, the fluorinated product was isolated and its structure was confirmed by ^1H NMR and ^{19}F NMR.

3. Results and discussion

3.1. Cyclic voltammetry

Typical cyclic voltammetry (CV) responses for compound **1a** at different sweep rates in CH_3CN/TBAP are presented in Fig. 1(A). Three distinct anodic peaks are

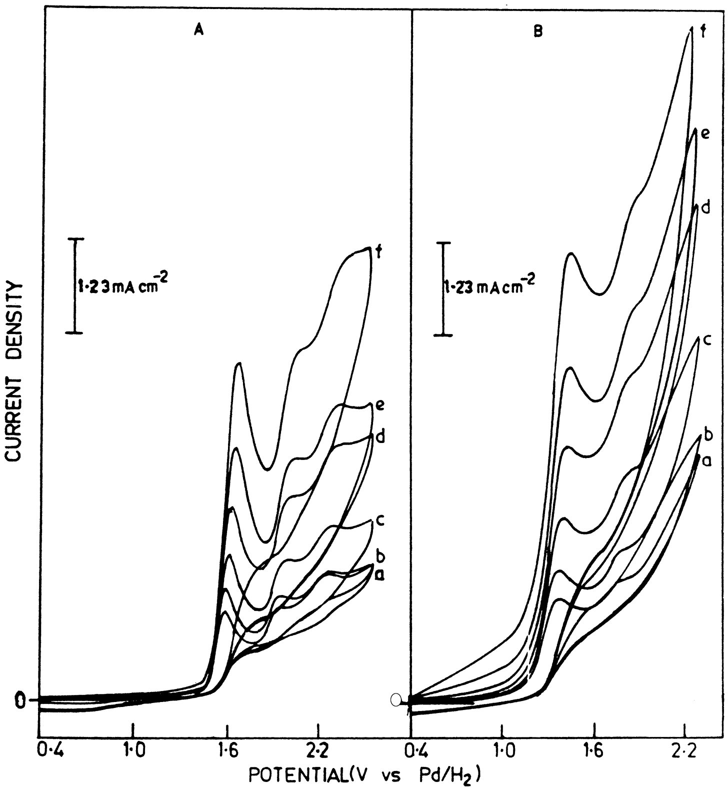


Fig. 1. Cyclic voltammograms for the oxidation of 4 mM of $C_6H_5SCH_2COOCH_3$ on Pt in CH_3CN (A) 0.1 M TBAP and (B) $Et_3N{\cdot}3HF$ at different scanning speeds (v) (mV s^{-1}). (a) 20, (b) 40, (c) 80, (d) 160, (e) 320, and (f) 640.

noticed. All the anodic peaks are found to increase with sweep rates (Fig. 1(A)) and concentration of reactant. In all respects, the CV responses obtained for **1a** are similar to voltammetric responses obtained earlier for arylsulfides [13,14]. In CH_3CN/TBAP other compounds (**2a–8a**) also showed similar behaviour. Hence, the general oxidative mechanistic pathway discussed for arylsulfides [13,14] also should hold good for the arylsulfides containing active methylene groups currently investigated here. This is confirmed by the present voltammetric investigation.

Compared to the CH_3CN/TBAP system, the $CH_3CN/Et_3N\cdot 3HF$ system gives slightly lower anodic limit. Significant background oxidation current is always noticed beyond 2 V in $CH_3CN/Et_3N\cdot 3HF$ medium. Typical CV for compound **1a** in $Et_3N\cdot 3HF$ medium are presented in Fig. 1(B). The anodic peak current is slightly higher in this medium (compare Fig. 1(A) and Fig. 1(B)). The oxidation peak potential is also shifted to a slightly less positive region. Similar patterns in the CV responses were also noted for compounds **2a–8a** in $CH_3CN/Et_3N\cdot 3HF$. In this medium since the back-ground itself increases beyond 2 V, the third anodic peak observed in CH_3CN/TBAP is not distinctly visible (compare Fig. 1(A) and Fig. 1(B)).

The anodic peak potentials and peak current values for all the eight compounds **1a**–**8a** are summarised in Table 1. The first anodic peak potential is generally found to shift to less positive values indicating that the oxidation process proceeds more easily in $CH_3CN/Et_3N\cdot 3HF$ and the peak current is found to be higher in $CH_3CN/Et_3N\cdot 3HF$ when compared to CH_3CN/TBAP (Table 1). The general voltammetric patterns are also similar. Hence, one may presume that the active site for the initial oxidation of the reactant is the same in CH_3CN/TBAP as well as $CH_3CN/Et_3N\cdot 3HF$ media, namely the –S– atom. This observation supports the Pummerer mechanistic pathway (Scheme 1) suggested earlier for similar compounds.

Generally the peak current in CH_3CN/TBAP as well as in $CH_3CN/Et_3N\cdot 3HF$ is found to increase with increase in concentration. The relative variation in the peak current values depends significantly on the nature of individual compounds. The compounds for which the $i_{\mathrm{pal}'}$ values in $CH_3CN/Et_3N\cdot 3HF$ medium are significantly higher also give higher yields in SEF (see later). The individual first anodic peak current values for the four compounds investigated here do not show a linear dependence on molecular size or molecular weight (Table 1, Fig. 2) as would be expected for a simple diffusion controlled process. This suggests a predominant role for adsorption or relative rate of chemical steps.

Compounds **8a** is an exception to the general trends outlined as shown in Fig. 3. For this compound, i_{pal} in CH_3CN/TBAP is always considerably higher than the $i_{\mathrm{pal}'}$ value in $CH_3CN/Et_3N\cdot 3HF$ medium (Fig. 3). The compound exhibits significant adsorption effects in CV measurements. With increase in concentration, for example the CV shows a sharp drop beyond the anodic peak potential value in the later medium alone (Fig. 4). At 10 mM concentration levels, for example, in multisweep, voltammograms, the anodic peak current decreases significantly in second and subsequent sweeps. The electrode requires repeated cleaning after each voltammetry recording to ensure reproducibility.

3.2. *Preparative electrolysis*

For compounds which do not show blocking type of adsorption during constant current electrolysis when the overall cell voltage would remain fairly stable except for a small increase due to concentration over-voltage. A typical cell voltage vs. time curve for $PhSCH_2COOMe$ is shown in Fig. 5 (curve a). In cases where blocking type adsorption is predominant, the active surface area $(1-\theta)$ continuously decreases as surface coverage due to insulating film (θ) develops. The cell voltage-time response for compound **8a** ($PhSCH_2COOPh$) under identical conditions for example, increases from 3 V to nearly 7 V during electrolysis (Fig. 5 Curve b).

Under ideal conditions, passage of charge for a $2F + 0.4F$/mol reaction should lead to the monofluoro derivative. But, HPLC data shows that in most cases, two product peaks correspond to monofluoro as well as difluoro derivative. For compound **8a**, HPLC shows multi peaks with poor reproducibility. The molar yield of monofluoro derivative, difluoro derivative and total yield for all the eight

Table 1
Oxidation peak potentials and peak currents of sulfides containing active methylene group, $PhSCH_2R$

No.	Sub. no.	Substrate	E_{pal} (V)		i_{pal} (mA cm^{-2})	
		[R]	TBAP/CH_3CN	$Et_3N.3HF/CH_3CN$	TBAP/CH_3CN	$Et_3N.3HF/CH_3CN$
1.	**1a**	COOMe	1.62	1.46	3.27	4.43
2.	**2a**	$COOC_6H_4$-Cl-*P*	1.84	1.72	2.71	3.75
3.	**3a**	$CONCH_6H_4$-Cl-*p*	1.63	1.63	1.50	3.06
4.	**4a**	$COOC_6H_4$-NO_2-*p*	1.76	1.62	2.78	2.94
5.	**5a**	$CONH_2$	1.71	1.57	1.64	2.17
6.	**6a**	$CONHC_6H_4$-NO_2-*p*	1.69	1.52	1.58	2.11
7.	**7a**	$CONHC_6H_5$	1.71	1.48	1.48	2.46
8.	**8a**	$COOC_6H_5$	1.69	1.04	3.69	1.07

I_{pal} – first anodic peak current, E_{pal} – first anodic peak potential, S.R. = 40 mV/sec, Concentration = 10 mM.

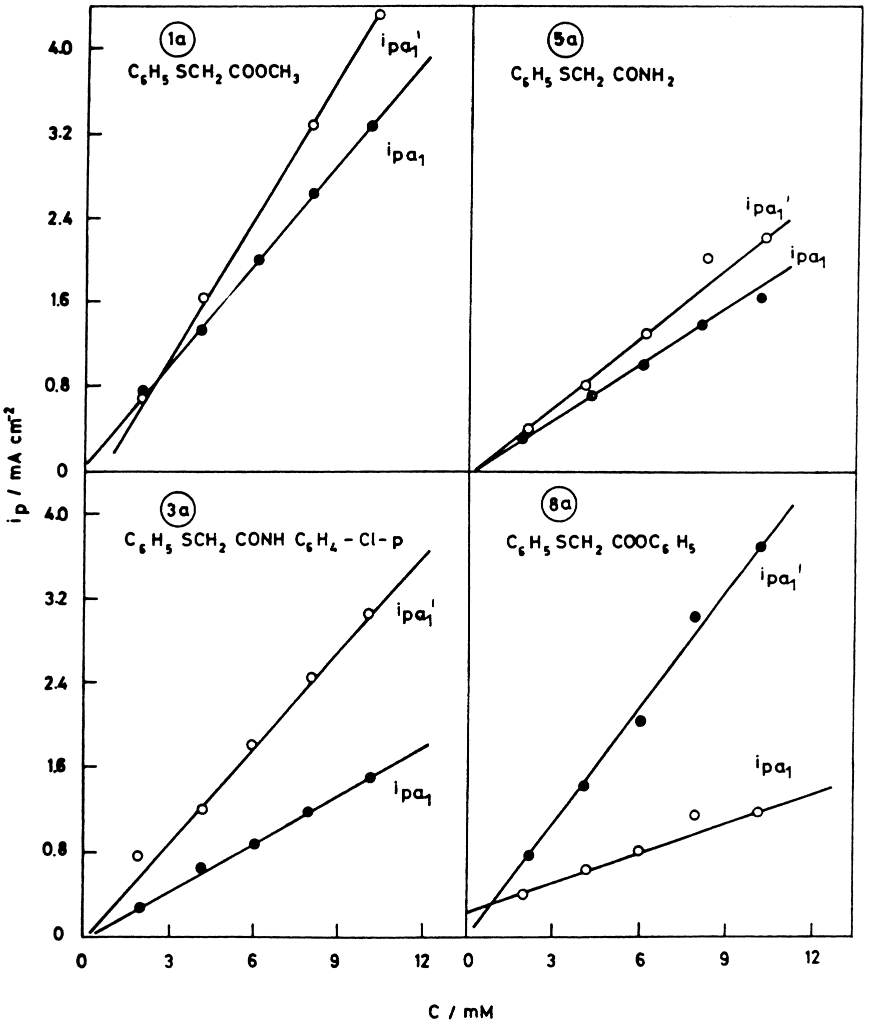


Fig. 2. Plots of i_p vs. C of sulfides containing active methylene group [**1a**–**8a**] where i_{pal} is peak current in 0.1 M TBAP/CH_3CN and $i_{pal'}$ in 0.1 M $Et_3N.3HF$/CH_3CN.

compounds are summarise in Table 2 and their ^{19}F characteristics in Table 3.

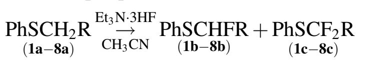
Sufficient charge for a 2F + 0.4F/mol reaction was passed for all compounds. However, except for compound **1a**, difluoro derivative (corresponding to 4F/mol reaction) is found to be the predominant product. This may be due to the blocking type of adsorption and/or polymerisation by a competitive pathway. The concentration of reactant avail-

Table 2
Selective electrofluorination of sulfides containing active methylene groups

No.	Sub. No.	Sulfides	Average cell voltage (V)	Product yield[a]		Total yield	Unreacted substrate
				b	*c*	*b* + *c*	
1.	**1a**	COOMe	3.80	72	5	77	2
2.	**2a**	$COOC_6H_4$-Cl-*p*	5.10	12	56	68	–
3.	**3a**	$CONHC_6H_4$-Cl-*p*	5.20	7	56	63	–
4.	**4a**	$COOC_6H_4$-NO_2-*p*	5.00	6	50	56	14
5.	**5a**	$CONH_2$	4.70	22	27	49	22
6.	**6a**	$CONHC_6H_4$-NO_2-*p*	5.10	6	36	42	5
7.	**7a**	$CONHC_6H_5$	5.80	6	28	34	10
8.	**8a**	$COOC_6H_5$	7.00	17	10	27[b]	14

[a] – Yield from HPLC.

[b] – Multiple peaks.



$$\underset{(\mathbf{1a}\text{–}\mathbf{8a})}{PhSCH_2R} \xrightarrow[CH_3CN]{Et_3N\cdot 3HF} \underset{(\mathbf{1b}\text{–}\mathbf{8b})}{PhSCHFR} + \underset{(\mathbf{1c}\text{–}\mathbf{8c})}{PhSCF_2R}$$

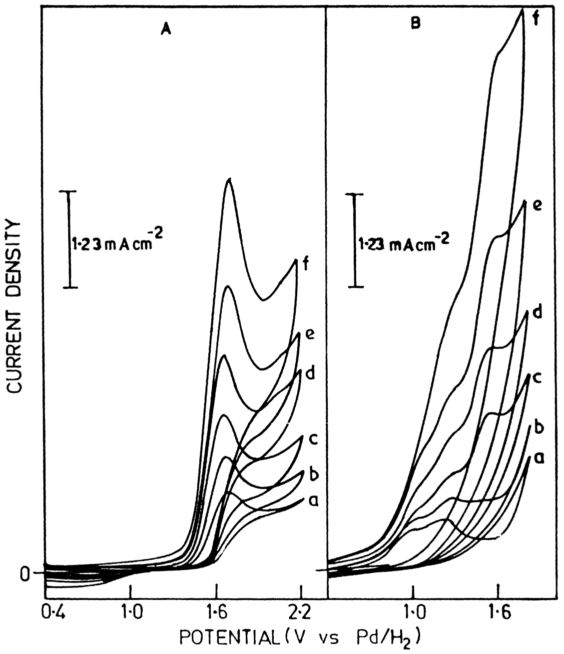


Fig. 3. Cyclic voltammograms for the oxidation of 4 mM of $C_6H_5SCH_2COOC_6H_5$ on Pt in CH_3CN (A) 0.1 M TBAP and (B) $Et_3N.3HF$ at different v ($mV\ s^{-1}$) (a) 20, (b) 40, (c) 80, (d) 160, (e) 320, and (f) 640.

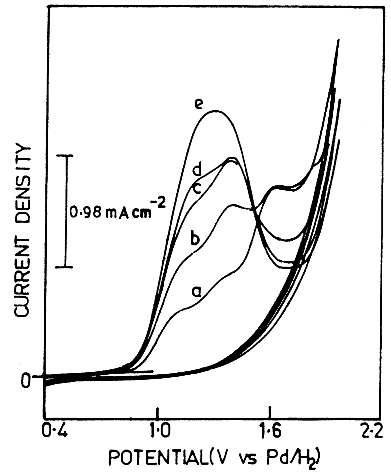


Fig. 4. Cyclic voltammograms for the oxidation of $C_6H_5SCH_2COOC_6H_5$ at Pt in CH_3CN containing 0.1 M $Et_3N.3HF$ at different concentrations (mM), $v = 40\ mV\ s^{-1}$. (a) 2, (b) 4, (c) 6, (d) 8, and (e) 10.

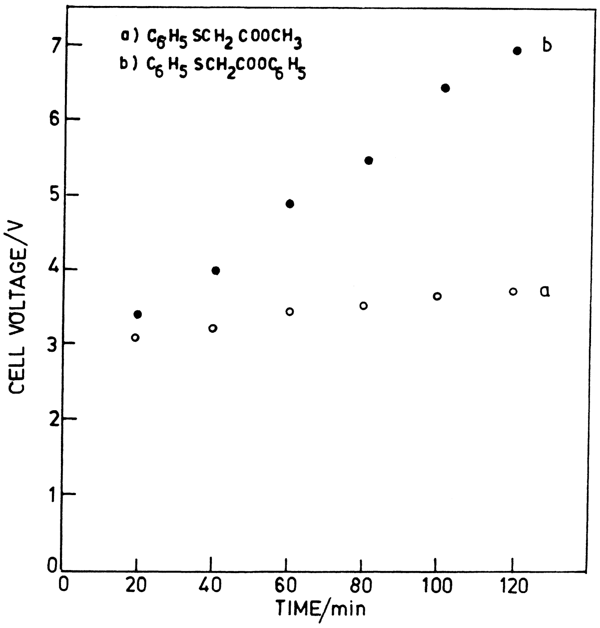


Fig. 5. Plots of cell voltage vs. time of (a) $C_6H_5SCH_2COOCH_3$ and (b) $C_6H_5SCH_2COOC_6H_5$ during the constant current electolysis in 0.3 M $Et_3N.3HF/CH_3CN$.

Table 3
^{19}F NMR characteristics of products

	^{19}F NMR of products (ppm)	
Sub. no. (a)	Monofluoro (b)	Difluoro (c)
1a	−160.7 (d, 1F, J = 52 Hz)	−83.3 (s, 2F)
2a	−158.7 (d, 1F, J = 52 Hz)	−84.0 (s, 2F)
3a	−157.6 (d, 1F, J = 52 Hz)	−82.9 (s, 2F)
4a	−161.2 (d, 1F, J = 52 Hz)	−84.1 (s, 2F)
5a	−160.3 (d, 1F, J = 52 Hz)	−83.4 (s, 2F)
6a	−161.7 (d, 1F, J = 52 Hz)	−83.6 (s, 2F)
7a	−158.3 (d, 1F, J = 52 Hz)	−82.3 (s, 2F)
8a	–	–

able for fluorination would be considerably lower than the initial concentration taken and the charge passed per actual mole of reactant available for fluorination is considerably higher than the charge required for a 2F reaction leading to the formation of difluoro derivative. T. Fuchigami et al. also suggested an influence of insulating polymer film on the product distribution pattern [17] and J. Simonet et al. have indicated that this blocking type of adsorption is absent for α-(phenylthio)derivatives containing alkyl groups attached to methylene and electron withdrawing substituents in the phenyl ring [11,12]. The results of the present study (Table 2) show that a adsorption effect can also be lower for some compounds containing more than one phenyl group.

3.3. *Comparison of results of cyclic voltammetry (CV) and preparative electrolysis*

Cyclic voltammetry (CV) data presented in Table 1 clearly suggest that the peak currents are not related to molecular size and molecular weight as noted above (Table 2). The anodic peak potential in presence of $CH_3CN/Et_3N{\cdot}3HF$ varies between 1.45 and 1.72 V except for compound **8a** where the first anodic peak is noted around 1.0 V (Table 1). The compounds such as $PhSCH_2COOMe$ and $PhSCH_2COOPh$ which give the highest yield and lowest yield, respectively (Table 1) also show significant deviations from the linear relationship (Fig. 6).

Quite interestingly, much better correlation between the first anodic peak current and the total molar yield was found

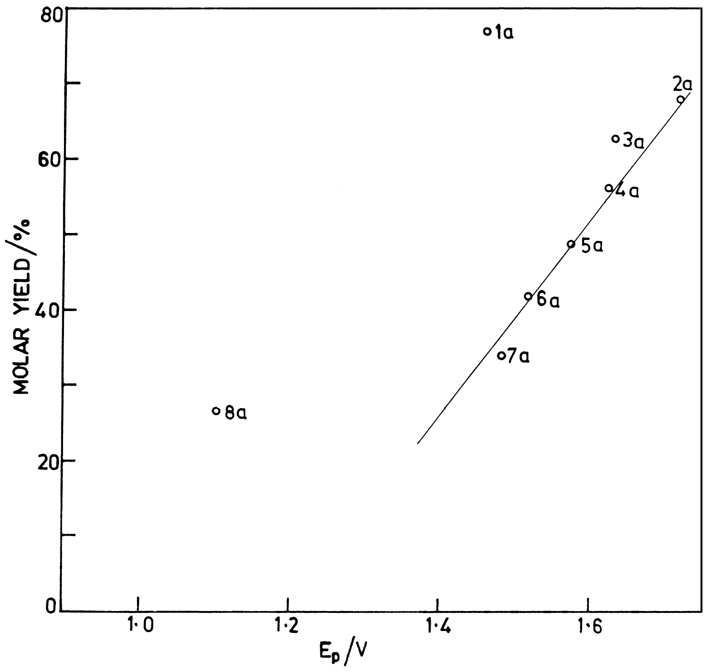


Fig. 6. Plots of E_p (10 mM, 40 mV s^{-1}) vs. molar yields of $PhSCH_2CONHR$ and $PhSCH_2COOR$ where R = [**1a**–**8a**].

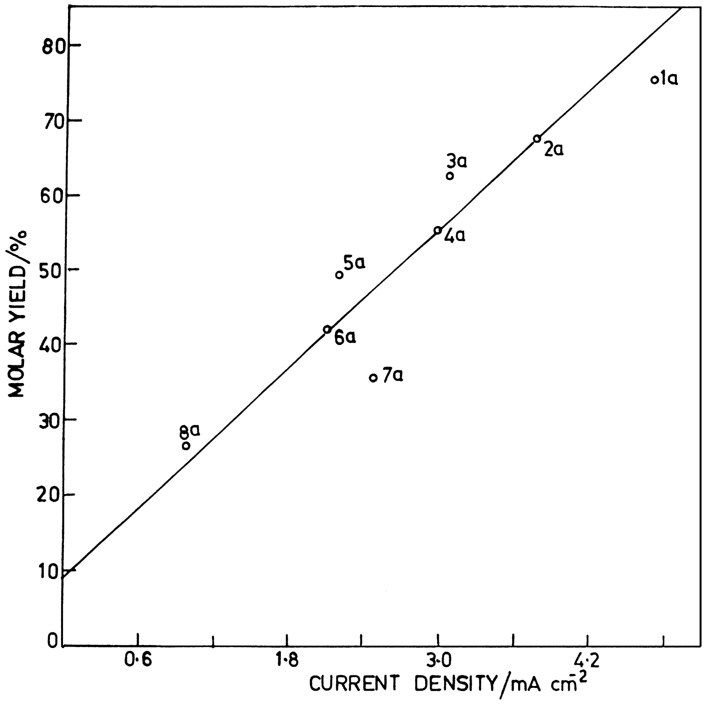


Fig. 7. Plots of i_p (10 mM, 40 mV s^{-1}) vs. molar yields of $PhSCH_2CONHR$ and $PhSCH_2COOR$ where R = [**1a**–**8a**].

for all the eight compounds (**1a**–**8a** as shown in Fig. 7). The higher the first anodic peak current, the better the observed yield. This confirms the view that the formation of insulating film by adsorption decreases the anodic peak current in CV and the overall yield in preparative electrolysis. The exact cause for the adsorption effect or the correlation between the molecular structure and adsorption is not clear.

Two observations on the structure-synthetic yield correlation may be made. In general, α-(phenylthio)acetates undergo more efficient fluorination when compared to α-

(phenylthio)acetamide derivatives. Compared to the substituted phenyl rings, unsubstituted phenyl rings in the acetates as well as amide derivatives exhibit strong inhibitive adsorption effects and hence very low overall yield due to their large molecular size and molecular weight.

4. Conclusions

Cyclic voltammetric responses of sulfides containing active methylene groups in $CH_3CN/Et_3N\cdot 3HF$ are similar to those obtained in conventional CH_3CN/TBAP medium suggesting that the SEF also proceeds through the sulfide cation radical route termed as the Pummerer mechanism. However, adsorption properties of individual compounds influence the overall yield efficiency of SEF significantly. Reactants which show little blocking type adsorption behaviour in voltammetric studies, invariably lead to high yields of monofluoro derivatives. In preparative electrolysis, wherever blocking type of adsorption predominates, the overall molar yield was found to be low and difluoro derivatives were predominant. An interesting direct correlation between cyclic voltammetric peak currents and overall molar yields of products was obtained for all the compounds involved. This suggests the possibility of ascertaining the synthetic potentiality of reaction from preliminary cyclic voltammetric results.

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