Effect of solvents on the selective electrofluorination of aromatic compounds containing active methylene groups

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Abstract

Voltammetry and constant current electrolysis was used to study the oxidative fluorination of $PhSCH_2COOMe$, $PhSCH_2CONH_2$, $PhSCH_2COOPh$ and $PhCH_2CN$ in solvent-free $Et_3N \cdot 3HF$ and $Et_3N \cdot 3HF$ dissolved in CH_3CN, THF, DME and sulfolane. Sulfolane, DME and THF containing $Et_3N \cdot 3HF$ show much lower oxidation limits when compared to $CH_3CN/Et_3N \cdot 3HF$. These compounds undergo simultaneous oxidation along with background oxidation processes. Solvent-free $Et_3N \cdot 3HF$ has a much wider anodic potential range for the oxidation of organic compounds. Selective electrofluorination of $PhSCH_2COOMe$ and $PhSCH_2COOPh$ does not show significant solvent effects. THF and DME were found to be more efficient for the selective fluorination of $PhSCH_2CONH_2$ and $PhCH_2CN$ compared to CH_3CN. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Selective electrofluorination; Active methylene compounds; Solvent effects

1. Introduction

CH_3CN has been the solvent of choice for selective electrofluorination, but other solvents such as sulfolane [1], and methylene chloride [2,3] have also been used. There are few reports on the effect of different solvents on selective electrochemical fluorination processes [4–6]. Acetonitrile (CH_3CN), dimethoxy ethane (DME) and tetrahydrofuran (THF) appear to be good solvents for this purpose. Dimethyl formamide (DMF) and dioxane have also been evaluated. The efficiency of fluorination in methylene chloride appears to depend on the nature of the compound involved [2]. The solvent-free supporting electrolytes namely $Et_3N \cdot 3HF$ [7–10], $Et_4NF.nHF$ [11,12] and py.nHF [13–15] themselves may also be employed as the electrolytic medium for selective electrofluorination.

In the present study, the following compounds which show widely different behaviour in $CH_3CN/Et_3N \cdot 3HF$ medium as reported earlier [16,17] are chosen to assess the influence of solvent on their selective electrochemical fluorination behaviour. Methyl α-(phenylthio)acetate ($PhSCH_2COOMe$) undergoes efficient selective fluorination in $CH_3CN/Et_3N \cdot 3HF$ whereas α-(phenylthio)acetamide ($PhSCH_2CONH_2$) gave rather poor yields. Phenyl α-(phenylthio) acetate ($PhSCH_2COOPh$) undergoes strong adsorption

which inhibits further electrochemical oxidative fluorination in $CH_3CN/Et_3N \cdot 3HF$ [16,17]. Phenylacetonitrile ($PhCH_2CN$) does not show a distinct oxidation peak in $CH_3CN/Et_3N \cdot 3HF$ [1].

The selective electrochemical fluorination of these compounds was carried out in sulfolane, THF and DME containing 1 M $Et_3N \cdot 3HF$. In addition, $Et_3N \cdot 3HF$ itself was also evaluated as the solvent-supporting electrolyte system for these compounds. The anodic potential limits in these solvent supporting electrolyte media and the voltammetric behaviour of these compounds in such media are also reported in this work.

2. Experimental details

The purity of the samples was checked by HPLC (Shimadazu LC 8-A) with Shim–Pack (4.0 mm×25 cm) ODS column which has absorbance at 254 nm and 100% methanol as eluent. ^{1}H NMR spectra were taken with a Brucker NMR spectrometer at 90 MHz with tetramethysilane (TMS) as internal standard and $CDCl_3$ as solvent. ^{19}F NMR spectra were taken with a Brucker 80 CY NMR spectrometer at 75.4 MHz with $CFCl_3$ as standard and $CDCl_3$ as solvent.

THF and CH_3CN (HPLC grade), sulfolane and DME (AR grade) were obtained from SRL, India. $Et_3N \cdot 3HF$ was prepared by mixing Et_3N and anhydrous HF (AHF) at

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low temperatures. Tetrabutylammonium perchlorate (TBAP) was kept in a dessicator. Phenylthio compounds such as $PhSCH_2COOMe$, $PhSCH_2CONH_2$ and $PhSCH_2$-$COOPh$ were prepared and have been characterised [18]. $PhCH_2CN$ was obtained from SRL, India.

Cyclic voltammetry was done in an undivided cell with Pt wire as working electrode, Pt foil counter electrode and Pd/H_2 reference electrode at $25\pm1^\circ C$ [16]. $Et_3N\cdot3HF$ itself was used as supporting electrolyte. The electrochemical cell was fabricated using high density polypropylene. A single compartment polypropylene cell of 50 ml capacity with a tight fitting Teflon cover with provision for working, counter and reference electrodes and a gas inlet were used. The immersed portion of the N_2 gas inlet tube used for deaeration, was made of fluoroethylene polypropylene (FEP).

Electrolysis was carried out at Pt anode and cathode (9 cm^2). The required quantity of $Et_3N\cdot3HF$ (0.3 M for CH_3CN and 1 M for other solvents) was dissolved in the selected solvents under dry conditions. To eliminate possible presence of moisture, pre-electrolysis was carried out at 3.0 V. During the time of preparative electrolysis, polarity reversal was applied between the electrodes (time interval 10 s positive and 10 s negative). After the electrolysis, Na_2CO_3 solution was added to the electrolyte until the pH was neutral. The solution was poured into 200 ml of water and extracted with ether. The ether layer was washed with brine (150 ml), ether evaporated and the residue was dried over anhydrous $MgSO_4$. Purity and hence the yield of fluoro compound was calculated using HPLC with CH_3OH as eluent.

3. Results and discussion

3.1. Cyclic voltammetric investigations

Initially, cyclic voltammograms were recorded in all the solvent-supporting electrolyte systems chosen in the absence of reactant molecules to study the background current levels and anodic potential limits. (Table 1). The anodic potential limit in solvent-free $Et_3N\cdot3HF$ for example is only slightly lower than the conventional O.1 M TBAP/CH_3CN system. In CH_3CN, even 0.1 M $Et_3N\cdot3HF$ was found to be sufficient to give a fairly conducting medium with satisfactory anodic limits of 2.54 V (Table 1). How-

Fig. 1. Cyclic voltammograms for the oxidation of 50 mM of $PhCH_2CN$ on Pt in $Et_3N\cdot3HF$ at different V (mV s^{-1}): (a) 20; (b) 40; (c) 80; (d) 160; (e) 320.

ever, in all the other three solvents, namely sulfolane, DME, and THF, a minimum of 1.0 M $Et_3N\cdot3HF$ was found to be necessary to obtain satisfactory conductivity. In these three media, the anodic limit was also found to be low (Table 1). In general, the anodic background current was found to increase with increasing concentration of $Et_3N\cdot3HF$.

In solvent-free $Et_3N\cdot3HF$, even active methylene compounds without an –S– atom, such as $PhCH_2CN$ show well-defined voltammetric responses (Fig. 1). A distinct irreversible anodic peak is noticed around 2.1 V. The anodic peak current is found to increase with square root of sweep rate and concentration. Typical cyclic voltammograms of $PhSCH_2COOMe$ in solvent-free $Et_3N\cdot3HF$ systems are shown in Fig. 2. The cyclic voltammograms are quite similar to those obtained in $CH_3CN/Et_3N\cdot3HF$ [16,17]. The oxidation peak potential, however, is shifted by 300 mV towards the less positive region. It may thus be concluded that $PhSCH_2COOMe$ undergoes more facile oxidation in solvent-free $Et_3N\cdot3HF$ when compared to $CH_3CN/Et_3N\cdot3HF$. The oxidation processes, however, are quite similar in both media. A similar conclusion may also be drawn regarding the voltammetric behaviour of $PhSCH_2CONH_2$.

The cyclic voltammograms of $PhSCH_2COOPh$ in solvent-free $Et_3N\cdot3HF$ exhibit the sharp anodic peaks which are typical of strong reactant adsorption. For this compound, polishing of electrode becomes absolutely necessary between each voltammetric recording to ensure reproducibility. The effect of blocking adsorption is also clearly noticed in multisweep cyclic voltammograms. In the second and subsequent sweeps, the anodic peak current falls

Table 1
Anodic limits for solvent-supporting electrolytes on Pt electrodes

No.	Solvent-supporting electrolyte systems	Anodic potential limit at 2 mA cm^{-2}
1	0.1 M TBAP/CH_3CN	2.82
2	$Et_3N\cdot3HF$	2.62
3	0.1 M $Et_3N\cdot3HF$/CH_3CN	2.52
4	1.0 M $Et_3N\cdot3HF$/sulfolane	1.90
5	1.0 M $Et_3N\cdot3HF$/THF	1.46
6	1.0 M $Et_3N\cdot3HF$/DME	1.22
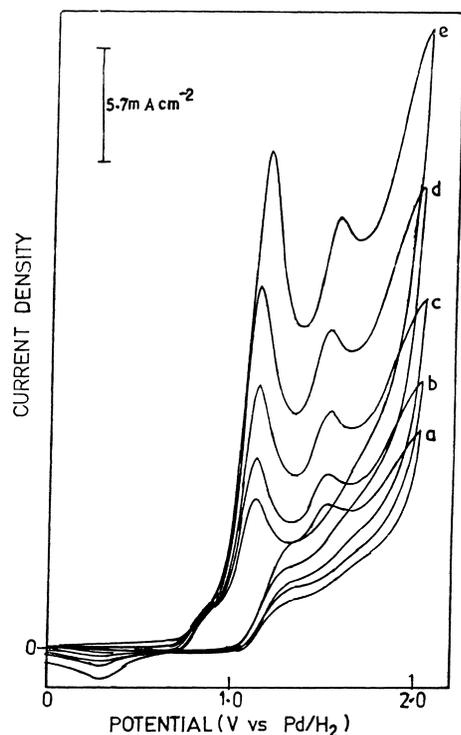
Fig. 2. Cyclic voltammograms for the oxidation of 50 mM of PhSCH$_2$COOMe on Pt in Et$_3$N·3HF at different V (mVs^{-1}): (a) 20; (b) 40; (c) 80; (d) 160; (e) 320.

significantly. Quite similar blocking of adsorption effects for this compound was also noticed in CH$_3$CN/Et$_3$N·3HF medium [16,17].

3.2. Preparative electrolysis

Since distinct oxidations peaks are not noticed in sulfolane, DME and THF, it is difficult to select the anodic potential for constant potential electrolysis. Hence, constant current electrolysis was carried out for all the four compounds mentioned above in the four supporting electrolyte systems under otherwise identical conditions. A constant charge of 2F/mol with current density of 15 mA/cm^2 was passed. The monofluoro products obtained from the four compounds were confirmed by ^{1}H NMR and ^{19}F NMR. The spectroscopic data were found to agree well with literature values of PhSCHFCOOMe, PhSCHFCONH$_2$, PhSCHF-COOPh [19] and PhCHFCN [20]. The results obtained are summarised in Tables 2 and 3. Table 2 summarises the overall yield obtained in each solvent-supporting electrolyte system. This parameter can also be affected by polymerisation and further lead to difluoro derivative. The percentage of unreacted substrate in the product mixture for each experiment based on HPLC data are summarised in Table 3. The following generalised conclusions may be drawn from these tables.

Compounds such as PhSCH$_2$COOMe, which undergoes quite efficient selective fluorination in CH$_3$CN/Et$_3$N·3HF medium itself, also appears to behave well in other solvent-supporting electrolyte systems. The overall yield for the compound, for example, is above 50% in all the given media.

For compounds such as PhSCH$_2$COOPh, which show strong adsorption and polymerisation effects in CH$_3$CN/Et$_3$N·3HF medium [16,17], variation of solvent supporting electrolyte system results in very little improvement in yield

Table 2

Selective electrofluorination of active methylene containing compounds in different solvent-supporting electrolytes

No.	Substrate (5 mmol)	Yields (%)				
		0.1 M Et$_3$N·3HF	1.0 M Et$_3$N·3HF			Et$_3$N·3HF
		CH$_3$CN	Sulfolane	THF	DME	
1	PhSCH$_2$COOCH$_3$	72	63	64	51	59
2	PhCH$_2$CN	24	60	58	69	54
3	PhSCH$_2$CONH$_2$	22	53	72	66	18
4	PhSCH$_2$COOPh	17	32	10	22	19

Table 3

Percentage of unreacted material at the end of electrolysis during the selective electrochemical fluorination of active methylene containing compounds in different solvent-supporting electrolytes

No.	Substrate (5 mmol)	Unreacted materials (%)				
		0.1 M Et$_3$N·3HF	1.0 M Et$_3$N·3HF			Et$_3$N·3HF
		CH$_3$CN	Sulfolane	THF	DME	
1	PhSCH$_2$COOCH$_3$	2	21	21	23	13
2	PhCH$_2$CN	43	20	15	10	39
3	PhSCH$_2$CONH$_2$	22	9	0	0	50
4	PhSCH$_2$COOPh	14	50	10	56	40

and efficiency. The yield of monofluoro compound does not exceed 30% in any of the solvent-supporting systems investigated.

Hence, the solvent-supporting electrolyte system appears to be important only in those cases wherever the yield in $CH_3CN/Et_3N\cdot3HF$ is low and polymerisation and adsorption effects are also low. In these cases, solvent supporting electrolyte systems have a profound influence on the overall yield and efficiency. $PhCH_2CN$ and $PhSCH_2CONH_2$ are the typical cases in this category. In the case of $PhCH_2CN$, all the solvent-supporting electrolyte systems give higher yields of monofluoro derivative, when compared to $CH_3CN/Et_3N\cdot3HF$. In the case of $PhSCH_2CONH_2$, sulfolane, THF and DME are found to be the better solvents for efficient selective electrochemical fluorination.

The present experimental results, however, are not significantly broad to understand the exact cause for the widely different effects of solvent-supporting electrolyte systems on the overall yield and efficiency. Many solvent properties can influence the overall efficiency. Some possible causes are solubility of reactants, stability of cation radicals generated in the solvent, the nucleophilicity of the solvent, molecule and the solubility of fluorinated product in the solvent-supporting electrolyte system.

4. Conclusion

The present investigation suggests that $Et_3N\cdot3HF$ exhibits poor electrolytic conductivity in solvents other than CH_3CN. Hence a minimum of 1 M $Et_3N\cdot3HF$ is necessary for voltammetric study as well as preparative electrolysis in these media. The voltammetric investigations in solvent-free $Et_3N\cdot3HF$, in the present study, indicate broad similarities between the voltammetric behaviour of all these compounds in this medium and in $CH_3CN/Et_3N\cdot3HF$. The oxidative mechanistic pathway does not appear different in these two media. The yield and efficiency of these compounds are, however, influenced significantly by the solvent-supporting electrolyte system used. In the case of more easily oxidisable compounds ($PhSCH_2COOMe$) and more easily polymerisable molecular species ($PhSCH_2$-COOPh), solvent supporting electrolyte system exert little influence on the overall yield and efficiency.

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