

Selective electrofluorination of phenylacetonitrile and α -(phenylthio)acetonitrile — the role of sulfur and other operating parameters

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Received 4 February 1998; accepted 1 June 1998

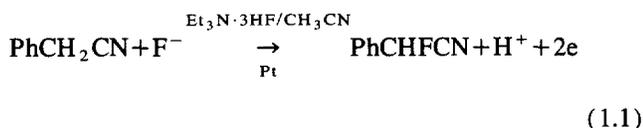
Abstract

Cyclic voltammetric and constant current electrolysis were employed to study the electrochemical fluorination of PhCH_2CN and PhSCH_2CN in $\text{Et}_3\text{N} \cdot 3\text{HF}/\text{CH}_3\text{CN}$ using Pt electrodes. The presence of a sulfur atom near the methylene group in PhSCH_2CN ensures the oxidative fluorination of this compound at much lower potential (around 1.75 V) when compared to PhCH_2CN (2.0 V in solvent-free $\text{Et}_3\text{N} \cdot 3\text{HF}$). Operating parameters such as drying the solvent, pre-electrolysis, polarity reversal, temperature, current density, and concentration of HF as well as Et_3N in CH_3CN medium show significant influence on the overall yield of more easily oxidisable PhSCH_2CN when compared to PhCH_2CN . Maximum yields of 23% in the case of PhCHF_2CN and 61% in the case of PhSCH_2F were achieved. © 1998 Elsevier Science S.A. All rights reserved.

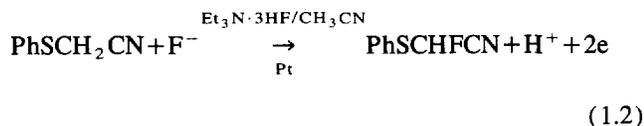
Keywords: Selective electrofluorination; Phenylacetonitrile; α -(Phenylthio)acetonitrile

1. Introduction

The conventional selective electrochemical fluorination route [1] is of considerable current interest specifically in the area of side chain active methylene groups [2]. Fluorination of phenylacetonitrile (PhCH_2CN) led to 20% yield of α -(fluoro phenyl)acetonitrile (PhCHF_2CN) [3].



Sulfur containing α -methylene compounds like α -(phenylthio)aceto-nitrile (PhSCH_2CN) were generally found to give much better yields of PhSCH_2F [4].



It was of interest to compare the voltammetric behaviour as well as preparative yields of these two compounds under widely different operating conditions to understand the role

of sulfur in selective electrochemical fluorination. Operating parameters [5] such as chemical or electrochemical drying of solvent-supporting electrolyte system [6], constant current/constant potential electrolysis [7], current interruption techniques [3,5,8–12], concentration of Et_3N as well as HF in CH_3CN medium [13–16] and presence/absence of trace level water [17] are known to have significant influence on the selective electrochemical fluorination process.

2. Experimental

The purities of samples were checked by HPLC [Shimadzu LC 8-A] with Shim-pack (4.0 mm \times 25 cm) ODS column which has absorbance at 254 nm and 100% methanol as eluent. ^1H NMR spectra were taken with a Bruker NMR spectrometer at 90 MHz with tetramethylsilane (TMS) as internal standard and CDCl_3 as solvent. Fluorine NMR spectra were taken with a Bruker WP 80 CY NMR Spectrometer at 75.4 MHz with CFCl_3 as standard and CDCl_3 as solvent. Positive shifts were designated as negative.

PhCH_2CN was obtained from SRL, India. PhSCH_2CN was prepared by the coupling reaction of thiophenol with chloroacetonitrile in the presence of sodium [18]. Cyclic voltammetry was performed as previously described [19].

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Electrolysis was carried out at Pt anode and cathode (area of 9 cm^{-2}) at $25 \pm 1^\circ\text{C}$ under a dry N_2 atmosphere. Chemical drying was attempted by stirring the solvent-supporting electrolyte system with anhydrous LiF (which removes water through hydration) and filtering off the solid particles just before use. Polarity reversal at 10-s intervals under galvanostatic conditions was achieved by employing a locally made timer instrument.

After electrolysis ($2 + 0.2 \text{ F/mole}$), the solution was neutralised with aqueous ammonia and acetonitrile was evaporated. The residual liquid was poured into 100 ml of water and extracted with ether. The ether layer was washed with brine solution (200 ml), ether evaporated and the contents dried over anhydrous MgSO_4 . Presence of mono as well as difluoro derivatives were confirmed by ^1H and ^{19}F NMR and the yield by HPLC.

3. Results and discussions

3.1. Cyclic voltammetry

Typical cyclic voltammograms of the $\text{Et}_3\text{N} \cdot 3\text{HF}/\text{CH}_3\text{CN}$ in the absence and in the presence of PhCH_2CN are presented in Fig. 1a,b respectively. PhCH_2CN does not exhibit any distinct voltammetric peak below 2.2 V where oxidation of the solvent-supporting electrolyte system commences. This appears to be the main reason for very low yield and efficiency of selective electrofluorination of PhCH_2CN in this medium [20]. A distinct oxidation peak for PhCH_2CN was indeed found at about 2.0 V only in CH_3CN free $\text{Et}_3\text{N} \cdot 3\text{HF}$ (Fig. 1d). The solvent free $\text{Et}_3\text{N} \cdot 3\text{HF}$ medium is recommended for selective fluorination of compounds such as PhCH_2CN that are difficult to fluorinate [16,21,22].

Typical cyclic voltammograms of PhSCH_2CN at different concentrations are shown in Fig. 2. Two distinct anodic peaks are present. The voltammetric responses are quite similar to those for arylsulfides in which the first oxidation peak is attributed to the oxidation of the sulfur atom leading to the generation of a cation radical ^+S [23]. This suggests the involvement of the sulfur atom in the oxidative fluorination processes, through the Pummerer mechanism involving ^+S rather than direct electrochemical oxidation involving active methylene centre [24]. Higher yields of monofluoro derivative obtained in the preparative electrolysis of PhSCH_2CN when compared to PhCH_2CN (Section 3.3) are also connected with the sulfur atom (Scheme 1).

Typical linear voltammetric responses of PhSCH_2CN in 0.1 M $\text{Et}_3\text{N} \cdot 3\text{HF}/\text{CH}_3\text{CN}$ containing 0–0.5 M water are shown in Fig. 3. With increase in water content, the first anodic peak potential becomes more positive. The background wave, on the other hand becomes more negative. These observations suggest that water can significantly influence the oxidative fluorination of the active methylene compounds. This can occur through direct competitive oxidation of a water molecule or through nucleophilic attack by a cation radical

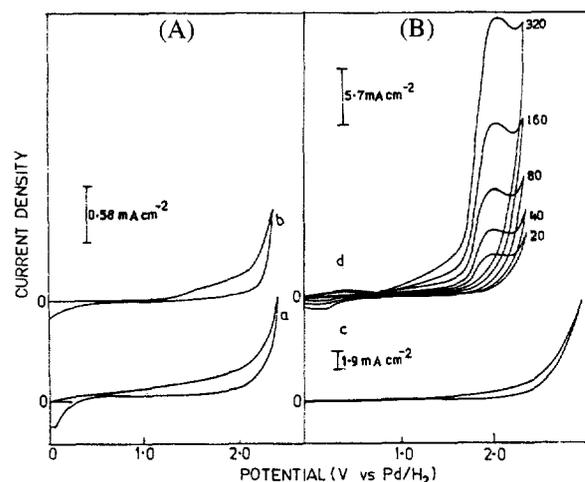


Fig. 1. Cyclic voltammograms on Pt in (A) 0.1 M $\text{Et}_3\text{N} \cdot 3\text{HF}/\text{CH}_3\text{CN}$; (B) CH_3CN free $\text{Et}_3\text{N} \cdot 3\text{HF}$; (a), (c) in the absence of PhCH_2CN and (b), (d) in the presence of 50 mM PhCH_2CN at $\nu = 40 \text{ mV s}^{-1}$.

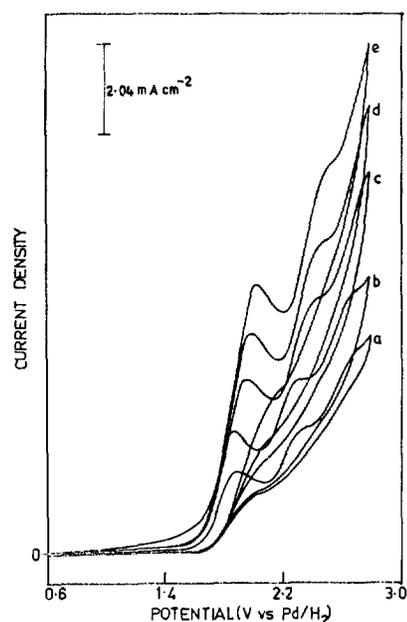
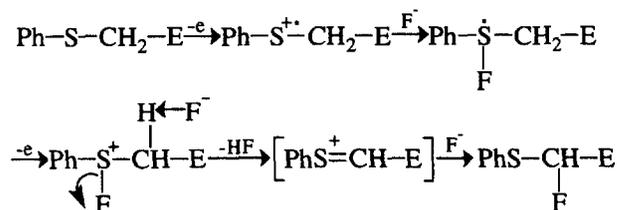


Fig. 2. Cyclic Voltammograms for the oxidation of PhSCH_2CN on Pt in CH_3CN containing 0.1 M $\text{Et}_3\text{N} \cdot 3\text{HF}$ at different concentrations (mM): (a) 2; (b) 4; (c) 6; (d) 8; and (e) 10; $\nu = 40 \text{ mV s}^{-1}$.



Scheme 1. Pummerer mechanism [24].

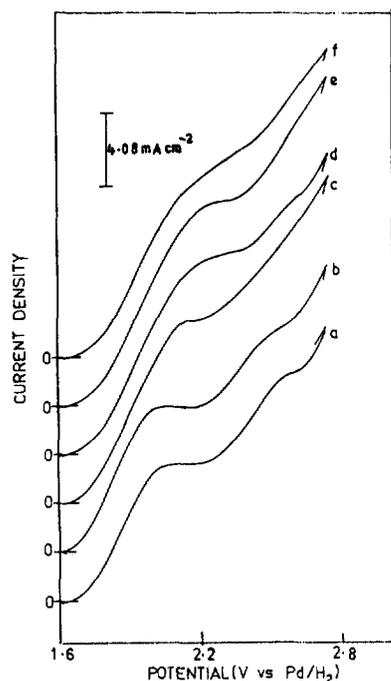


Fig. 3. Effect of water on the oxidation of 10 mM of PhSCH₂CN on Pt in CH₃CN containing 0.1 M Et₃N·3HF at $v = 40 \text{ mV s}^{-1}$. Concentration of water (moles): (a) 0; (b) 0.1; (c) 0.2; (d) 0.3; (e) 0.4; and (f) 0.5.

generated from the reactant species [16]. Water attack as a nucleophile may either lead to the formation of a sulfoxide and sulfone [17] or formation of free radicals that may undergo further polymerisation [16].

3.2. Product identification in preparative electrolysis

After preparative electrolysis of PhCH₂CN, a new doublet with coupling constant J , of 47 Hz is seen at δ -value of 5.9 in the ¹H NMR spectrum. This corresponds to a –CHF– group. The corresponding proton signal of phenyl ring is also shifted downfield. Fluorine NMR data of the product also confirms this. ($\delta = 168.0$, d, $J = 47.0$ Hz), literature value for PhCHF₂CN $\delta = 168.3$, $J = 47.0$ Hz [3].

The presence of PhSCF₂CN cannot be directly observed from ¹H NMR signals. However, an indirect estimate of the

ratio of mono fluoro and difluoro derivative is possible by quantitative comparison of –CHF– and Ph ring proton signals. The significantly higher phenyl proton signal when compared to –CHF– signal (> 5:1) clearly suggests the presence of the difluoro derivative in the mixture. Further confirmation of the presence of –CF₂– and –CHF– groups in the product mixture is obtained from ¹⁹F NMR. The signal at $\delta = 84.5$ corresponds to –CF₂– and the signal at $\delta = 154.6$ corresponds to –CHF– doublet, ($J = 49.0$ Hz), literature value for PhSCF₂CN $\delta = 83.4$ [12], and for PhSCHFCN $\delta = 152.0$, d, $J = 49.0$ Hz [12].

3.3. Effect of operating parameters on the yield and selectivities

Preparative electrolysis of PhCH₂CN and PhSCH₂CN were carried out under various operating conditions and the products were isolated and characterised under identical experimental procedures using predominantly HPLC for data analysis.

The effect of LiF treatment as a drying step, pre-electrolysis and polarity reversal individually and in various combinations on the yield of the corresponding monofluoro derivatives are summarised in Table 1. In addition to the yield obtained from HPLC data, the conversion yield data based on the reactant consumed is also presented. The effect of LiF treatment, however, is found to be marginal, especially in the case of PhCH₂CN. Polarity reversal and pre-electrolysis are equally effective in improving the yield of fluoro derivatives and the combination of these methods always leads to the same or slightly better conversion under all the experimental conditions. The yield and conversion efficiency of PhSCH₂CN is considerably higher than that of PhCH₂CN. This suggests that the selection of the compounds based on the ease of electrochemical oxidation is always of predominant importance. Other operating parameters can only improve the general trend in the yield and conversion efficiencies.

The effect of pre-electrolysis voltage and solvent supporting electrolyte composition on the yield and conversion efficiency of both the compounds are summarised in Table 2.

Table 1
steps on the selective electrochemical fluorination of PhCH₂CN and PhSCH₂CN in 0.3 M Et₃N·3HF/CH₃CN

No.	Trace level water removal steps	Yield (%)		Unreacted material (%)	
		PhCHF ₂ CN	PhSCHFCN	PhCH ₂ CN	PhSCH ₂ CN
(1)	LiF treatment and filtration (2 g)	2	29	68	44
(2)	Preelectrolysis (3.0 V)	15	30	32	44
(3)	Polarity reversal (10 s, +ve; 10 s, –ve)	14	29	37	31
(4)	LiF treatment + preelectrolysis	12	35	56	16
(5)	LiF treatment + polarity reversal	20	37	43	26
(6)	Preelectrolysis + polarity reversal	22	33	43	36
(7)	LiF treatment + preelectrolysis + polarity reversal	23	61	43	22

Conditions: substrate taken: 5 mmol; current density: 15 mA cm^{-2} ; temperature: $25 \pm 1^\circ\text{C}$; electrolysis time: 2 h. Average cell voltage for PhCH₂CN: 3.0 to 8.0; average cell voltage for PhSCH₂CN: 3.0 to 3.4.

Table 2

Effect of pre-electrolysis and supporting-electrolyte concentration on the selective electrofluorination of PhCH₂CN and PhSCH₂CN

No.	Pre-electrolysis cell voltage (V)	Concentration of electrolyte (M)	Yield (%)		Unreacted material (%)	
			PhCHF ₂ CN	PhSCH ₂ CF ₂ CN	PhCH ₂ CN	PhSCH ₂ CN
(1)	2.5	0.3	3	29	92	39
(2)	3.0	0.3	23	61	43	22
(3)	4.5	0.3	–	13	58	80
(4)	3.0	0.15	–	12	47	81
(5)	3.0	0.3	23	61	43	22
(6)	3.0	0.4	22	60	24	14
(7)	3.0	0.3 M Et ₃ N · 2HF	5	12	56	19
(8)	3.0	0.3 M Et ₃ N · 3HF	23	61	43	22
(9)	3.0	0.3 M Et ₃ N · 4HF	22	62	56	16

Conditions: substrate taken: 5 mmol; current density: 15 mA cm⁻²; temperature: 25 ± 1°C; polarity reversal: 10 s, +ve; 10 s, -ve; electrolysis time: 2 h. Average cell voltage for PhCH₂CN: 3.0 to 7.5; average cell voltage for PhSCH₂CN: 3.0 to 3.5.

Table 3

Effect of substrate concentration, temperature and current density on the selective electrofluorination of PhCH₂CN and PhSCH₂CN in 0.3 M Et₃N · 3HF/CH₃CN

No.	Concentration of substrate (mmol)	Current density (mA cm ⁻²)	Temperature (°C)	Yield (%)		Unreacted material (%)	
				PhCHF ₂ CN	PhSCH ₂ CF ₂ CN	PhCH ₂ CN	PhSCH ₂ CN
(1)	2.5	15	25	6	48	28	10
(2)	5.0	15	25	23	61	43	22
(3)	10.0	15	25	23	55	60	36
(4)	5.0	10	25	22	52	22	34
(5)	5.0	15	25	23	61	43	22
(6)	5.0	25	25	12	35	21	22
(7)	5.0	15	20	16	51	46	31
(8)	5.0	15	25	23	61	43	22
(9)	5.0	15	40	10	37	55	37

Conditions: polarity reversal: 10 s, +ve; 10 s, -ve; preelectrolysis: 3.0 V. Average cell voltage for PhCH₂CN: 3.0 to 8.2; average cell voltage for PhSCH₂CN: 3.0 to 3.4.

The results indicate that the preferable cell voltage for pre-electrolysis is about 3.0 V (inter-electrode distance of the cell is 2 cm). The preferred supporting electrolyte concentration is 0.3 M Et₃N · 3HF in CH₃CN.

The effect of reactant concentration, current density and temperature on the overall yield and conversion efficiency are summarised in Table 3. These results suggest that 5 mmol reactant concentration, 15 mA/cm⁻² current density, and 25 ± 1°C are the convenient operating parameters for efficient conversion of both the compounds.

In CH₃CN/Et₃N · 3HF under constant current electrolysis, the cell voltage for PhCH₂CN is found to increase continuously from 3.0 V at the beginning of electrolysis to as high as 8.1 V towards the end of electrolysis. This is predominantly due to the formation of an insoluble polymer film on the electrode surface. In the case of easily oxidisable compounds like PhSCH₂CN, such film formation effect is hardly noticed and the cell voltage varies only between 3.0 to 3.8 V during electrolysis. Thus, in such cases, it is also possible to pass electric charge substantially greater than 2.0 F/mole. This

leads to substantial increase in the yield of the difluoro derivative. This was confirmed by HPLC and NMR data [25].

4. Conclusions

The present investigation indicates that the efficiency of selective electrochemical fluorination depends to some extent on the ease of electrochemical oxidation of the reactant. Pre-electrolysis is preferably carried out at 3.0 V and current interruption/reversal techniques such as polarity reversal is certainly beneficial. Current density of 15 mA cm⁻² was generally found to be optimum and the process is less sensitive to temperature variations. The best supporting electrolyte concentration is 0.3 M Et₃N · 3HF. Under optimum conditions, maximum yields of 23% and 61% monofluoro derivative were obtained for PhCH₂CN and PhSCH₂CN, respectively.

Acknowledgements

One of the authors V.S thanks CSIR, New Delhi, for the award of fellowships. The authors also thank Volkswagen Stiftung, Germany for financial support of this work.

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