Ortho-carboxylate Effects in Copper-mediated Nucleophilic Substitution of Halothiophenecarboxylic Acids and Halobenzoic Acids with Sodium Bisulphite

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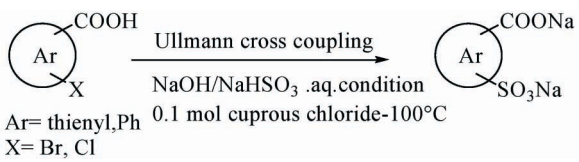
Ortho-carboxylate effects in Ullmann type nucleophilic substitution reactions were found to be much more pronounced as compared to those of other substituent and steric factors. In this study, we propose an *ortho* halogen assisted intramolecular oxidative addition-reductive elimination mechanism that fits our experimental observations. Experimental data has been generated with halothiophenecarboxylic acids and halobenzoic acids by performing copper-mediated nucleophilic substitution with scant referred sodium bisulphite as nucleophile under aqueous conditions. The novel mechanism was used to establish a new and improved process for preparation of monopotassium salts of 3-sulphothiophene-2-carboxylic acid, 2-sulphobenzoic acid, and 5-sulphothiophene-2-carboxylic acid. These monopotassium salts are critical intermediates and building blocks in the preparation of several therapeutically valuable drugs. The differences in reactivity between the halogens, chlorine and bromine was utilized to prepare aryl ethers including 2-acetyl-3-phenoxythiophene and 2-acetyl-3-(m-tolyloxy)thiophene that have not been reported in literature so far.

Keywords: *Ortho*-carboxylate effect; Ullmann type nucleophilic substitution; Intramolecular oxidative addition-reductive elimination; Sodium bisulphite.

INTRODUCTION

Unraveling the mechanism of modified Ullmann reactions has been of great interest to the scientific community ever since it was found that addition of relatively cheap ligands (diamines, amino alcohols, diketones, diols) made these reactions more efficient with catalyst amounts as low as 1 mol% or even lower.[1] These mechanisms require far milder conditions for known transformations compared to pre-existing methods. They also opened new avenues to heterocycle preparation and asymmetric synthesis.[2] It seems reasonable to expect that the mechanism of Ullmann type coupling reactions will vary, depending on the identity of the substrates, ancillary ligands and/or the reaction conditions. However, it has been established via several proposed mechanisms that the reaction between copper precursor complex and the nucleophile precedes the activation of the aryl halide.[1] Studies have indicated that such coupling reactions exhibit ortho-effects, a term by which we refer to the activation of chelating groups such as -NHCOR, -COOH, *ortho* to the aromatic halide.[1,3-5] The *ortho* carboxylate effects are pronounced even though the electronic substituent effects and ortho-alkyl steric effects are not.[6] Paine and Couture reported significant rate enhancements attributed to the *ortho* carboxylate effect in the Ullmann type nucleophilic substitution reaction.[7]

Scheme I Ullmann type coupling reaction



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Alkyl-3-chlorosulphonylthiophene-2-carboxylates are often used as key intermediates having several applications including preparation of therapeutically valuable drugs. They are also key intermediates in a range of active pharmaceutical ingredients (APIs),[8-14] and are prepared from the corresponding monopotassium salt of 3-sulphothiophene-2-carboxylic acids. These monopotassium salts are prepared according to Scheme I, via copper mediated nucleophilic substitution reaction with sodium bisulphite, followed by acidification and treatment with KCl.

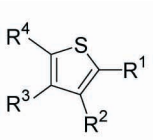
In this study we compare the rates of reaction of halothiophenecarboxylic acids and halobenzoic acids with sodium bisulphite in the quest to understand the *ortho*-carboxylate effects in copper mediated nucleophilic substitution reactions. Within the family of halothiophenecarboxylic acids, we present interesting results from comparing 3-chloro and 3-bromo thiophene analogs. The specific reagents discussed in this paper are labeled in Fig. 1. This investigation led to a new and improved process for the synthesis of monopotassium salt of 3-sulphothiophene-2-carboxylic acid (**3a**) and *ortho*-sulfobenzoic acid (**4g**). Further, we also present synthetic routes for monopotassium salt of 5-sulphothiophene-2-carboxylic acid (**3c**), 2-acetyl-3-phenoxythiophene (**5a**) and 2-acetyl-3-(m-tolyloxy)thiophene (**5b**). Finally we show that this experimental data validates our proposal of *ortho*-halogen assisted intramolecular oxidative addition – reductive elimination mechanism based on which these synthetic routes were developed.

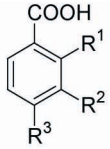
RESULTS AND DISCUSSIONS

The reaction conditions for copper mediated nucleophilic substitution of halogen by sodium bisulphite using 3-bromothiophene-2-carboxylic acid (**1b**) were optimized and it was chosen to be the model compound as described in the **Experimental section** (**General procedure**). A number of Lewis acid catalysts were screened including copper(I) chloride, silver nitrate, zinc chloride, nickel sulphate, lanthanum triflate, ytterbium triflate and palladium(II) acetate, palladium(II) acetate with ligand ± 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). Of the several Lewis acids and salts examined, cuprous chloride has been found to exhibit the best catalytic activity in facilitating nucleophilic substitution. Some copper species were found to be essential to catalyze this reaction, as the substitution did not take place in the absence of a copper catalyst.

Experiments with exclusively copper salts such as copper(I) chloride, copper(I) bromide, copper(I) iodide, copper(II) chloride, copper(II) triflate and copper in the form of copper bronze revealed that cuprous chloride exhibits better catalytic activity compared to the rest. Isomeric halothiophenecarboxylic acids and halobenzoic acids were subjected to Ullmann-type nucleophilic substitution (outlined in Scheme I) by sodium bisulphite under standard condition (Table 1).

Monopotassium salts **3a** prepared from 3-chlorothiophene-2-carboxylic acid **1a** typically require heating in autoclave at 140 °C for 16 hours which is quite drastic.[8] We





1a, R^1=COOH, R^2=Cl, R^3,R^4=H
1b, R^1=COOH, R^2=Br, R^3,R^4=H
1c, R^1=COOH, R^2,R^4=H, R^3=Br
1d, R^1=COOH, R^2, R^3=H, R^4=Br
1e, R^1=Br R^2=COOH, R^3,R^4=H
1f, R^1=COOH, R^2,R^3,R^4=H
1g, R^1=$COCH_3$, R^2=Br, R^3,R^4=H
1h, R^1=$COOCH_3$, R^2=Br, R^3,R^4=H
1i, R_2=Br, R_1,R_3,R_4-H
1j, R_1=$COCH_3$, R_2=Cl, R_3,R_4=H

2a, R^1=COONa, R^2=SO_3Na, R^3,R^4=H
2b, R^1=COONa, R^3=SO_3Na, R^2,R^4=H
2c, R^1=COONa, R^4=SO_3Na, R^2,R^3=H
2d, R^1=SO_3Na, R^2=COONa, R^3,R^4=H
3a, R^1=COOH, R^2=SO_3K, R^3,R^4=H
3b, R^1=COOH, R^3=SO_3K, R^2,R^4=H
3c, R^1=COOH, R^4=SO_3K, R^2,R^3=H
3d, R^1=SO_3K, R^2=COOH, R^3,R^4=H

4a, R^1=Br, R^2,R^3=H
4b, R^2=Br, R^1,R^3=H
4c, R^3=Br, R^1,R^2=H
4d, R^1=Cl, R^2,R^3=H
4e, R^2=Cl, R^3,R^4=H
4f, R^3=Cl, R^1,R^2=H
4g, R^1=SO_3K, R^2,R^3=H

Fig. 1. Thiophenecarboxylic acids, halobenzoic acids and other derivatives.

Table 1. HPLC reaction monitoring results

Entry	Starting material (SM)	HPLC Monitoring results*			Remarks
		Time	SM	Product	
1	**1a**	3 h	95.4	3.5	Very little reaction
2	**1b**	2 h	Nil	88.6	Fast reaction
3	**1c**	3 h	75.9	19.6	Slow reaction
4	**1d**	3 h	21.1	73.6	Faster than **1c**
		4 h	5.1	88.3	
5	**1e**	0.5	1.1	73.4	Faster reaction. More side product 1f is observed
6	**4a**	1 h	Nil	94.1	Very fast reaction
7	**4b**	3 h	86.6	3.2	Very little reaction
8	**4c**	3 h	89.4	10.3	Very little reaction
9	**4d**	3 h	75.6	22.7	Slow reaction
10	**4e**	3 h	99.7	Nil	No reaction
11	**4f**	3 h	99.9	Nil	No reaction
12	**1b**	3 h	22.8	62.3	2V water replaced by 2V of ethanol under standard conditions. Product has formed.
13	**1g**	3 h	96.1	Nil	2V water replaced by 2V of ethanol under standard conditions. No reaction.
14	**1h**	3 h	98.2	Nil	2V water replaced by 2V of ethanol under standard conditions. No reaction
15	**1a**	2 min	95.6	2.85	Microwave conditions, 80 °C, and 100W- No reaction
16	**1b**	2 min	4.9	68.8	Microwave conditions 80 °C, 100W, Product has formed. Better conversion as compared to **1a**.

* Yield is based on HPLC area percentage

discovered that bromo-acid **1b** undergoes cross coupling with sodium bisulphite under relatively milder conditions viz., 100 °C for 3 h under reflux conditions, as compared to chloro analog **1a** and thereby leading to a safe and scalable process for the preparation of **3a**.

Molecule **4g**, monopotassium salt of 2-sulphobenzoic acid, is a useful intermediate for the preparation of compounds with various applications.[15] Synthesis cited in literature start from *ortho*-chlorobenzoic acid **4d** via an Ullmann type nucleophilic substitution reaction with sodium sulphite, which requires conditions of 175 °C, under pressure in an autoclave for 24 h. However, our synthesis of **4g** starting from bromo acid **4a** required milder conditions viz., 100 °C for 2 h under reflux conditions.

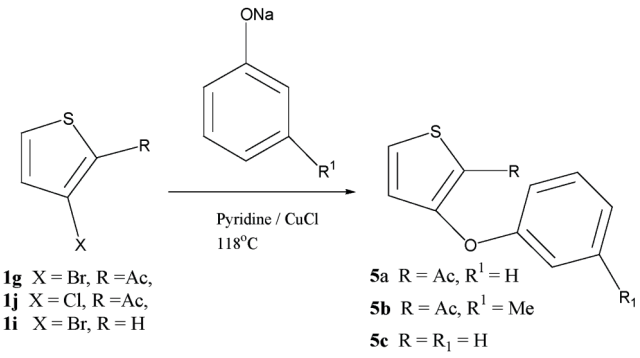
The chloro acid **1a** underwent only 4% reaction (Table 1, entry 1) under the standard conditions. The mono potassium salt **3a** (Table 1, entry 2, product) was isolated and characterized by spectral data. The molecule **3c** (Table 1, entry 4 product) was obtained from 5-bromothiophene-2-carboxylic acid **1d** under standard conditions and was characterized by spectral data. We have observed only 20% conversion in the case of **1c** (Table 1, entry 3), while **1d** exhibited a better reactivity, leading to 73% conversion in 3 h (Table 1, entry 4). We find that our results are consistent with data published by Luker et. al in the case of Pd catalyzed amination of electron deficient halothiophenes.[16] Between **1b** and 2-bromothiophene-3-carboxylic acid **1e**, **1e** displayed higher reactivity (Table 1, entry 5) but at the same time led to more hydro debromination product in comparison to that of **1b**. The order of reactivity of isomeric bromothiophene carboxylic acids, was found to be **1e** > **1b** > **1d** >> **1c**. Interestingly, the reaction of 2-bromobenzoic acid **4a**, with sodium bisulphite (Table 1, entry 6) was faster compared to that of **1b**.

The *meta* isomer **4b** (Table 1, entry 7) and *para* isomer **4c** (Table 1, entry 8) did not undergo substitution under standard conditions. Similarly amongst the three isomeric chlorobenzoic acids **4d**-**4f** (Table 1, entry 9, 10 & 11), only *ortho*-chloro isomer **4d** displayed some reactivity which was very low (23% conversion) compared to **4a** (>94% conversion). In the case of **4e** and **4f** there was hardly any reaction. In both *ortho*-bromo and *ortho*-chloro series,

halobenzoic acids exhibited higher reactivity compared to corresponding halothiophene carboxylic acids towards copper mediated nucleophilic substitution reaction with sodium bisulphite. To the best of our knowledge, such a comparative study of Ullmann type nucleophilic substitution of halobenzoic acids and halothiophene carboxylic acids with sodium bisulphite has not been reported in literature. The rate spread in the case of **4a** and **4c** was several folds greater compared to that of **1b** and **1d**. The bromides exhibited higher reactivity compared to the chlorides both in halobenzoic acids and halothiophene carboxylic acids. Under identical conditions, only **1b** (Table 1, entry 12) was found to be reactive while 3-bromo-2-acetylthiophene **1g** (Table 1, entry 13) and methyl-3-bromo-2-thiophenecarboxylate **1h** (Table 1, entry 14) did not undergo substitution. This reveals that substituent effect due to vicinal carboxylic acid group has an accelerating effect on the rate of the reaction. The high reactivity of **1b** over **1a** was also observed under microwave conditions (Table 1, entry 15 and 16).

The higher reactivity of bromo substituent when compared to chloro analogs in copper mediated cross coupling reactions was also observed in the preparation of phenolic ethers (Scheme II). The reaction with sodium phenoxide, in the case of bromo ketone **1g** was much faster compared to chloro ketone **1j**. After 8 h of reaction the bromo ketone **1g** showed 94.9% conversion (by HPLC area %) with 3.9% of starting material. Under identical conditions the reaction with **1j** showed only 53.4% conversion, with 45.3% of starting material. Under these conditions, 3-bromothiophene **1i** was hardly reactive (Table 2), the order of reactivity being **1g** >> **1j** > **1i**. Following this procedure, the aryl ethers, **5a** and **5b**, were prepared from **1g** and were characterized by NMR spectral data. To the best of our knowledge, these aryl ethers are not reported in literature. Interestingly, when the cross coupling reaction was performed with sodium sulphite (pH of the reaction mixture was around 10.5) instead of sodium bisulphite, but without adjusting the pH to 7.5, the reaction proceeded very well in 2 h resulting in complete consumption of starting material with 97.1% product formation, as monitored by HPLC. This observation indicates that the actual nucleophile might be the sulphite anion even in the case of reaction with sodium bisulphite at pH 7.5-7.7.

Scheme II Preparation of aryl ethers



1g X = Br, R =Ac,
1j X = Cl, R =Ac,
1i X = Br, R = H

5a R = Ac, R^1 = H
5b R = Ac, R^1 = Me
5c R = R_1 = H

Table 2. HPLC reaction monitoring of (Scheme II)

Entry	SM	Monitoring results HPLC area %			Remarks
		h	SM	Pdt	
1	**1i**	8	95	3.2	Very slow
		16	57	41	reaction.
		22	16.2	81.9	
2	**1j**	8	45.3	53.4	Slow reaction.
		16	15.6	82.8	
3	**1g**	8	3.9	94	Enhanced rate.
		16	0.2	95	

PROPOSED MECHANISM

Copper assisted nucleophilic substitution of aromatic halides can take place in a variety of ways.[17] Un-catalyzed pathways or Lewis acid promoted S_NAr, or *ipso* substitution, proceeding through addition-elimination mechanism can be ruled out on the basis of the following observations: i) Chloro analogs displayed very poor reactivity compared to the bromo analogs; ii) Other Lewis acids did not bring about coupling reaction and only Cu(I) was found to be an effective catalyst; iii) '*ortho*-carboxylate effects' causes high reactivity of *ortho* bromo carboxylic acid salts.

Elimination addition mechanism via an aryne intermediate can also be ruled out as there is no scope for formation of any hetero aryne intermediate in the case of **1b** and **1e**.[18] Any aryne intermediate generated by decarboxylative debromination cannot give rise to the observed products viz., *ortho*-sulfocarboxylic acids. Among the classes of mechanism that have been proposed in literature,[1,17,19] there are two conceivable ones involving 1) radical intermediates involving $S_{RN}1$ pathway, and 2) oxidative addition-reduction elimination. When Ullmann type nucleophilic substitution of **1b** with sodium bisulphite under standard con-

dition was performed in the presence of radical scavengers like molecular Oxygen or Tempo[20] we observed that part of sodium bisulphite was destroyed by these agents leading to incomplete reaction but the desired product was also formed. Interestingly, we found that *p*-dinitro benzene could not be used as radical scavenger in this reaction, as it was getting reduced to form *p*-nitro aniline under the reaction conditions. However when the experiment was performed in the presence of reagents like 2,6-di-tert-butyl-4-methyl phenol (BHT) or Tetrahydrofuran (THF) that are commonly employed as radical quenchers to probe $S_{RN}1$ mechanism,[21] the nucleophilic substitution reaction was not inhibited and expected product was formed. This observation clearly rules out $S_{RN}1$ mechanistic pathway. Our findings parallels the observations of Cirigotts, Ritch and Taylor who noted that silver nitrate, zinc chloride nickel chloride, Pd(II) chloride were completely ineffective catalysts for condensation of 2-bromobenzoic acid with benzoyl acetone in ethanolic sodium hydroxide.[22] They had observed that catalysis by some copper species was essential for this reaction.

Bowman et. al investigated the mechanism with respect to radical pathway and their experimental observations led to the inference that no aryl radicals are produced under copper(I) catalyzed conditions.[20] Further in contrast to the 3-bromo and 5-bromo isomers, the cuprous chloride catalyzed nucleophilic substitution reaction of 4-bromo thiophene-2-carboxyli acid **1c** with sodium bisulphite, was significantly very slow. The observed reactivity **1b** > **1d** >> **1c** cannot be accounted for by $S_{RN}1$ mechanism. Also the '*ortho*-carboxylate effect' observed in the case of **1b** cannot be rationalized on the basis of $S_{RN}1$ mechanism. We examined cyclic voltammeter data which revealed that bromo derivatives are reduced at more positive potential compared to chloro analogs (Fig. 2 and Fig. 3). The cathode peak potential for the C-Br bond reduction of **1b** and **1g** are observed at -1.882 V and -1.955 V respectively whereas the cathode peak potential for the C-Cl bond reduction of **1j** and **1a** are observed at -1.957 V and -2.058 V respectively. The results obtained from the above studies provided useful information with respect to the mechanism of reaction. The experimental findings are consistent with a cyclic *intramolecular oxidative addition-reductive elimination* mechanism operating in the case of **1b** as depicted in Scheme III and an intermolecular version in the case of **1d**. The intervention of oxidative addition-reductive elimination mechanism in Ullmann condensation was first proposed by Cohen[23] in 1974 and substantiated by follow-up studies from others,[19, 20, 24] indicating Cu(I) and Cu(III) are intermediates in this type of reactions. The exceptionally high catalytic activity of copper(I) thiophene-2-carboxylate in Ullmann type nucleophilic substitution reactions has been ascribed to the stabilization of the Cu(III) complex formed in the oxidative addition step thereby driving the equilibrium to the forward direction.[24] The proposed

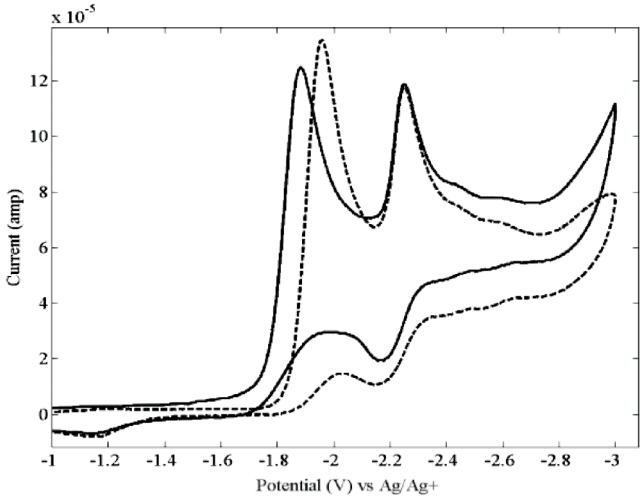


Fig. 2. Semi differentiated cyclic voltammogram of **1g** (solid line) and **1j** (broken line) at a scan rate of 0.5 Vs-1. The supporting electrolyte is TBAP (0.1 M) at glassy carbon electrode.

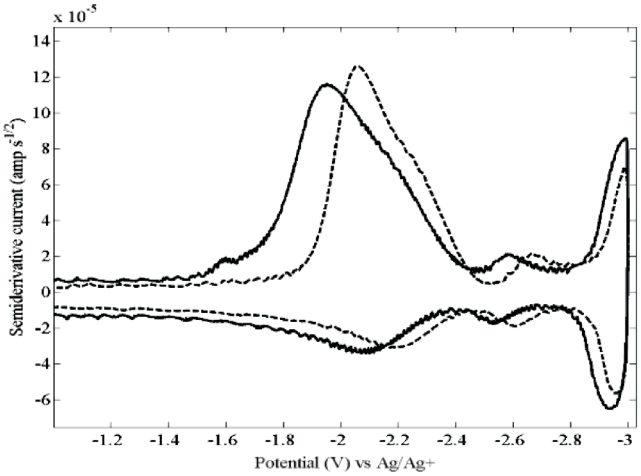
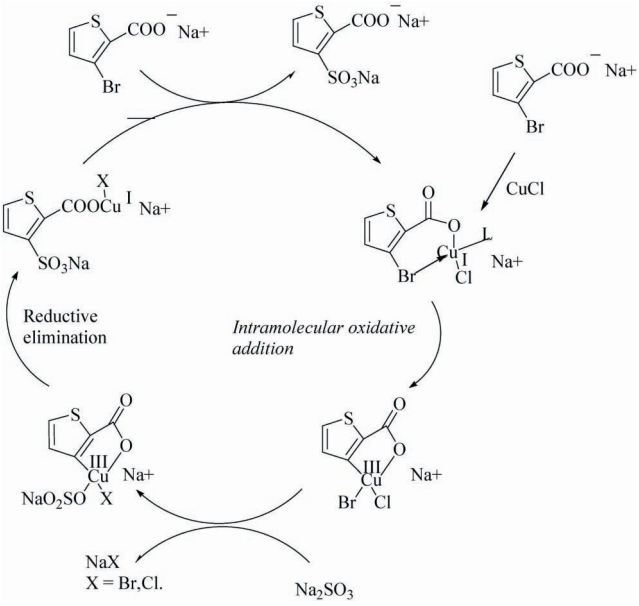


Fig. 3. Semi differentiated cyclic voltammogram of **1b** (solid line) and **1a** (broken line) at a scan rate of 0.5 Vs-1. The supporting electrolyte is TBAP (0.1 M) at glassy carbon electrode.

mechanism (Scheme III) is consistent with the following observations - 1) the reactivity order ArBr > ArCl parallels the leaving group ability of the halide ion; 2) Couplings are favored by electron withdrawing groups; 3) Coupling did not take place in the absence of copper catalyst; 4) There is a correlation between the cyclic voltametric data on cathodic potential and the leaving group ability of the halide; 5) Free radical inhibitors like BHT or THF did not suppress the reaction. From the observed order of reactivity, viz., **4a** >> **4b** ≥ **4c** and **1e** > **1b** > **1d** >> **1c**, it is evident that the very high reactivity exhibited by the *ortho*-bromo carboxylic acids **1b**, **1e** and **4a** in comparison with other isomers is primarily due to chelation of copper(I) carboxylate with the adjacent bromine atom and also due to mesomeric interaction of the bromine with the carboxylate group. This chelation in the case of **1b**, **1e** and **4a**, makes the oxidative addition step an intramolecular process and as a consequence renders it more facile.

Scheme III Cyclic *intramolecular oxidative addition-reductive elimination* mechanism



The mesomeric interaction of the bromine with the carboxylate group serves as an additional driving force for the oxidative addition in these cases. Thus mesomeric effect, high catalytic efficiency of copper(I) thiophene-2-carboxylate salts in Ullmann coupling reactions and chelation resulting in proximity of copper species combindly provides an unusual driving force for the *intramolecular* oxidative addition of Cu(I) ion to the C-Br bond in the case of **1b**.[24] The mesomeric effect evidently is more important than simple chelation as revealed by the observed order of reactivity **1b** > **1d** >> **1c**. Though **1b** is more reactive than **1d**, the rather high reactivity exhibited **1d** however cannot be solely due to mesomeric interaction since it's aromatic counterpart *p*-bromobenzoic acid **4c** did not display such high reactivity compared to the *ortho* isomer **4a**. An intermolecular oxidative addition promoted by thiophene-2-carboxylate function in the case of **1d** can account for the observed higher rate order as compared to its aromatic analog **4c** where in such type of activation does not exist. The reactivity of **1b** < **1e** and **4a**, may be due to a possible chelation of carboxylate copper with sulphur atom in the case of **1b** (Scheme IV), while this sort of chelation does not exist in the case of **1e** and **4a**.

Scheme IV Chelation with sulphur atom

The first direct observation of Cu(I)-Cu(III) redox steps relevant to Ullmann type coupling reaction has very recently been provided by Alicia Casitas, Amanda King et. al.[25] The very high reactivity of bromo acid **1b** compared to those of bromo ester **1h** and bromo ketone **1g** again highlights the role of *ortho*-carboxylic acid group in tremendously accelerating the Ullmann type nucleophilic substitution reaction.

CONCLUSION

In summary for the first time we have carried out an investigation on copper catalyzed nucleophilic substitution by sodium bisulphite on halothiophenecarboxylic acids and halobenzoic acids. This methodology provides a convenient route for the synthesis of aryl and heteroaryl sulfonic acids. This is particularly effective for the preparation of aromatic and heteroaromatic *ortho*-sulfocarboxylic acids. Our study of reactivity of isomeric bromothiophene carboxylic acids and isomeric bromobenzoic acids towards this copper catalyzed nucleophilic substitution reaction with sodium bisulphite has brought out the importance of chelation as well as mesomeric effect in accelerating this nucleophilic substitution reaction. The bromo acid **1b** was

used to achieve a scalable process for the preparation of **3a**. This concept was extended towards synthesis of aryl ethers **5a** and **5b**, which have so far not been reported in literature. We have also proposed a mechanism based on halogen assisted cyclic intramolecular oxidative addition–reductive elimination to explain the greater reactivity of the *ortho*-bromobenzoic acid, 2-bromo-thiophene-3-carboxylic acid and 3-bromo-thiophene-2-carboxylic acid. We have, for the first time, reported the comparative work between thiophene and benzenoid systems and also proposed a rationale for the higher *ortho*-carboxylate effect in the case of aromatic halocompounds as compared to thiophene analogs.

EXPERIMENTAL SECTION

Materials and Methods

3-Bromothiophene-2-carboxylic acid **1b** was prepared from 3-bromothiophene purchased from M/s Modipro India Pvt Ltd, Mumbai. 3-chlorothiophene-2-carboxylic acid **1a** was made from 3-chlorothiophene, purchased from M/s Modipro India Pvt Ltd, Mumbai. All other reagents and solvents were from commercial sources and used without purification. HPLC – in process check analysis was carried out using Phenomenex Luna C18, 25 cm × 4.6 mm; ID 5 µm or equivalent. Mobile phase Methanol: Water: TFA: TEA = 1500:500:1:0.5 v/v; wavelength-254 nm, flow rate 1 mL per minute.

Melting points were taken in VEEGO-programmable apparatus. FT IR spectra were recorded in the solid state as KBr pellet using Perkin-Elmer instrument, scanning in the range 4400-450 cm^{-1}. GC-Mass analysis-QP2010-Shimadzu instrument. LC-MS analysis – LCQ DECA XP PLUS-Thermo Finnegan instrument Proton NMR and ^{13}C NMR spectra were measured in $CDCl_3$ using Bruker, 300 MHz instrument and the chemical shifts are reported in δ ppm relative to TMS. Microwave reactions were performed in Discover Benchmate model instrument. Cyclic Voltametric data was derived from IIT Madras. CH 660A Electrical work station is used. Working electrode – Glassy carbon. Reference electrode-Ag/Ag^+. Counter electrode-Pt electrode. Supporting electrode-Tetrabutylammonium perchlorate. Solvent-Acetonitrile. Scan rate-0.1 V/s.

General procedure for sodium bisulphite substitution reaction

The substrate was dissolved in one equivalent of aq NaOH (10% w/w). Sodium bisulphite aq. solution (1.15 equivalent of 37% w/w) was added. The pH was adjusted to 7.5-7.7 using aq. NaOH (30% w/w). 0.1 mole of cuprous chloride was added to the reaction mass and the mixture was heated to 100 °C. The reaction was monitored by HPLC. (Mobile phase Methanol: Water: TFA: TEA = 1500:500:1:0.5 v/v; wavelength-254 nm, flow rate 1 mL per minute). The reaction mass then worked up acidification and isolation of the corresponding potassium salt by treatment with KCl. The product was leeched with hot acetone.

Monopotassium salt of 3-sulfo-thiophene-2-carboxylic acid (3a) (Standard condition)

A solution of sodium bisulphite 118.6 g (1.14 mol in 320 mL DM water) was added to a clear solution of 3-bromo thiophene-2-carboxylic acid **1b** 207 g (1 mol), in aq. sodium hydroxide 40 g (1 mol in 400 mL of DM water) at room temperature. The pH of the mixture was adjusted to 7.5-7.7 using aq sodium hydroxide (30% w/w, 62 g of sodium hydroxide dissolved in 206 mL DM water). After pH adjustment, CuCl 10.35 g (0.1045 mol) was added and the solution was refluxed at 100 °C. The reaction was monitored by HPLC for the absence of bromo acid **1b**. The reaction was completed in 3 h. The mixture was cooled to room temperature and filtered under vacuum. Con.HCl 124 mL was added to the filtrate and the mass was heated to 90 °C. Solid potassium chloride 218.2 g (2.92 mol) was added in lots at 90 °C during 45 min. The reaction mixture was maintained at this temperature for 1 h and was slowly cooled to 0-5 °C. The reaction mixture was maintained at 0-5 °C for 12 h. The precipitated **3a** was filtered under vacuum .The product was dried at 110 °C for 3 hour. The dried material was heated with acetone (621 mL) under reflux for 30 min. The product was isolated by filtration and dried at 70 °C for 3 h to get monopotassium salt of 3-sulfo thiophene-2-carboxylic acid **3a** 209 g (85%) of HPLC purity >99% mp >250 °C. ^1H-NMR (300 MHz-DMSO-d_6) δ 7.828 (d, 1H, J = 4.8 Hz), 7.29 (d, 1H, J = 4.8 Hz), 14.83 (br s OH). ^{13}C NMR (300 MHz, DMSO-d_6) δ 129.63 (aromatic CH), δ 131.52 (aromatic CH), δ 132.10 (aromatic Cq), δ 147.73 (aromatic -Cq), δ 161.01 (-COOH), DEPT spectrum. δ 129.63 (aromatic CH), δ 131.52 (aromatic CH).

Monopotassium salt of 5-sulfothiophene-2-carboxylic acid (3c)

Compound **3c** was prepared from 5-bromo thio-

phene-2-carboxylic acid **1d** in an analogous manner. 2 g of **1d** (9.66 mmol) gave 1.30 g (55%) of **3c**. White solid, mp >245 °C, HPLC purity 100%, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.14 (d, 1H, J = 3.67 Hz), 7.51 (d, 1H, J = 3.6 Hz), 13.414 (br s OH), ^{13}C NMR ($CDCl_3$) δ 126.2 (CH), 132.2 (CH), 133.2 (Cq), 157.4 (Cq), 163.3 (C=O); DEPT spectra δ 126.2 (aromatic CH), δ 132.2 (aromatic CH). LC-MS for the peak at RT 3.0 in HPLC. $(M-K)^+$ at *m/z* -207.3. HRMS-Mass M^+K -284.8706; Calc. mass = 284.8696.

Monopotassium salt of 2-sulfobenzoic acid (4g)

Compound **4g** was prepared from 2-bromo benzoic acid **4a**. 2 g (9.95 mmol) of **4a** gave 1.74 g (73%) of **4g**. White solid, mp >260 °C, ^{1}H-NMR (300 MHz-DMSO-d_6) δ 7.555 (m, 2H) δ 7.718 (dd, 1H, J = 1.5 Hz, J = 1.2 Hz), 7.849 (dd, 1H, J = 1.2 Hz, J = 1.2 Hz), 14.10 (br s OH). ^{13}C-NMR-(DMSO-d_6) δ in ppm, 126.56 (aromatic CH), 129.58 (aromatic CH), 130.63 (aromatic Cq), 130.68 (aromatic CH), 130.77 (aromatic CH), 144.08 (aromatic Cq) and 167.74 (carbonyl C), DEPT spectrum δ in ppm 126.56, 129.58, 130.68, 130.77 (aromatic CH).

2-Acetyl-3-phenoxythiophene 5a from 2-acetyl-3-bromothiophene 1g

Cuprous chloride (0.48 g, 4.85 mmol) and phenol (1.37 g, 14.58 mmol) were added sequentially to a solution of **1g** (1 g, 4.87 mmol) in dry pyridine (30 mL). Sodium hydride (0.6 g, 15 mmol, 60% dispersion in mineral oil) was then added slowly under nitrogen atmosphere. The reaction mixture was heated to reflux and monitored by HPLC, for reaction completion. Pyridine was removed under reduced pressure. The residue was diluted with ether (50 mL) and washed with 1N NaOH (3 × 30 mL), 1N HCl (2 × 30 mL) and 1N NaOH (30 mL). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under vacuum. The residue was chromatographed (hexane/3% ethyl acetate), to get **10b**, colorless liquid, yield 0.66 g (3.01 mmol 62%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.601 (s, 3H, CH_3), δ 6.617 (d, 1H, J = 5.4 Hz), δ 7.081 (d, 2H, J = 8.1 Hz), δ 7.168 (t, 1H, J_1 = 7.2 Hz, J_2 = 14.2 Hz), δ 7.368 (t, 2H, J_1 = 7.8 Hz, J_2 = 15.6 Hz), δ 7.474 (d, 1H, J = 5.4 Hz).

^{13}C NMR ($CDCl_3$) δ 24.23 (CH_3), 118.95 (Ar CH), 120.05 (Ar CH), 124.58 (Thiophene CH), 125 (Ar Cq), 127 (Thiophene Cq), 130 (Ar CH), 132.13 (Thiophene CH), 159.13 (Ar Cq), 190.22 (C=O), HRMS-M^+H; Mass 219.0481, Calc.mass-219.0480.

2-Acetyl-3-(m-tolyloxy)thiophene 5b

Similar process followed as in **5a**, Waxy solid Yield 55%.

^{1}H-NMR (300 MHz,$CDCl_3$) δ 2.36 (s, 3H, -Ar.CH_3), δ 2.595 (s, 3H, -CH_3) δ 6.615 (d, 1H, J = 5.7 Hz), δ 6.875 (d, 2H, J = 8.7 Hz), δ 6.988 (d, 1H, J = 7.5 Hz), δ 7.263 (t, 1H, J = 7.8 Hz), δ 7.465 (d, 1H, J = 5.7 Hz).^{13}C NMR ($CDCl_3$) δ 21.3 (Ar CH_3), 32.1 (CH_3), 118.95 (Ar CH), 119.3 (Ar CH), 119.4 (Thiophene Cq), 120.23 (Ar CH), 132.2 (Ar CH), 126.4 (Thiophene CH), 127 (Ar Cq), 130 (Thiophene CH), 140 (Ar Cq), 156 (Thiophene Cq), 193.22 (C=O), HRMS-HRMS M^+H-Mass-233.0634, Calc.mass-233.0636.

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