Efficient Synthesis of *N,N*-Disubstituted 5-Aminothiophene-2-carboxaldehydes by Nucleophilic Aromatic Substitution in Water

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Abstract: We have developed the first synthesis of *N,N*-disubstituted 5-aminothiophene-2-carboxaldehydes by Nucleophilic Aromatic Substitution of 5-bromothiophene-2-carboxaldehyde in water. This study shows selectivity between primary and secondary amines leading to the corresponding imines or amino derivatives respectively.

Since 1934 when Steinkopf reported the formation of colored reaction intermediates by reacting nitrothiophene with nucleophiles[1], Nucleophilic Aromatic Substitution (SNAr) at the thiophene ring has received much attention[2-21] and is an attractive method for introducing nucleophiles such as alkoxy[3-9], alkylthio[8,14, 21] or amino[6,8,14-18] groups at the thiophene ring.

In these SNAr reactions, the thiophene nucleus is generally substituted by one electron withdrawing group like nitro[3,6,16-18] or by a combination of a nitro group and other electron attracting functions like nitro[7,9], cyano[7,19], carboxylate[14,16,19], acetyl[8,14,19], trifluoromethanesulfinyl[4], carboxamido.[14,19] Leaving groups are usually halides[4,5,8,14,15,18] or methoxy[7,15,16] but also phenylsulfonyl[17,18] or nitrophenoxy.[17,18] The solvents used in these studies are benzene, toluene, xylene, methanol, dimethylsulfoxide, dimethylformamide or acetonitrile.

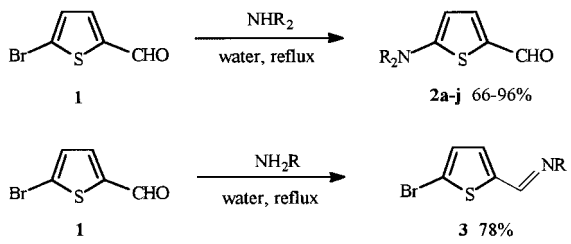
To our knowledge, only a few examples of SNAr on 5-bromothiophene-2-carboxaldehyde **1** by neutral nucleophiles have been reported. One by using a mixture of dimethyl (or diethyl) amine, dimethyl (or diethyl) ammonium bromide in methanol (or ethanol) followed by the hydrolysis of the intermediate imminium salt in basic media[22], others by refluxing the thiophene derivative with dibutylamine in xylene[23] and piperidine in DMSO.[24] These preparations afford 52, 49 and 81% respectively of the corresponding amino derivatives.

Indeed, polar solvents are useful in SNAr reactions but water, which is already used in various classes of reactions[25], to our knowledge has not been used so far in such reactions.

On the other hand, 5-dialkylamino-thiophene-2-carboxaldehydes have been obtained through electrophilic substitution on dialkylaminothiophenes. [26]

We describe here an easy, one step and high yielding access to various *N,N*-dialkyl and *N,N*-alkylarylaminothiophene-2-carboxaldehydes from the mildly activated 5-bromothiophene-2-carboxaldehyde **1** using water as a solvent.

Refluxing thiophene **1** in water with one equivalent of morpholine furnished the desired amino derivative **2a** in 38% yield (Table 1, entry 1). Increasing the amount of amine (2 or 3 equiv.) yielded 62 and 94% of substituted product respectively (entries 2, 3). These first experiments showed the feasibility of SNAr reactions in water on 5-bromothiophene-2-carboxaldehyde **1**, even mildly activated by a carboxaldehyde group (Scheme 1). The use of only 1.1 equivalent of the reacting amine is also possible without decrease of the yield (entries 4, 5) by adding 2 equivalents of a neutral base such as tributyl- or triethylamine. These experiments show that the reaction needs an excess of base to succeed.



Scheme 1

Table 1. Synthesis of *N,N*-disubstituted 5-aminothiophene-2-carboxaldehyde **2** in water[28]

Entry	Amine (eq.)	Additive (eq.)	Reflux (h)	2	Yield (%)[a]
1	morpholine (1)	none	24	**2a**	38
2	morpholine (2)	none	24	**2a**	62
3	morpholine (3)	none	12	**2a**	94
4	morpholine (1.1)	NBu_3 (2)	12	**2a**	91
5	morpholine (1.1)	NEt_3 (2)	12	**2a**	93
6	piperidine (3)	none	12	**2b**	96
7	dimethylamine (3)	none	12	**2c**	91
8	pyrrolidine (3)	none	12	**2d**	94
9	4-hydroxy piperidine (3)	none	12	**2e**	90
10	*N*-methyl 2-aminoethanol(3)	none	12	**2f**	90
11	dibutylamine (1.1)	NEt_3 (2)	12	**2g**	69
12	diphenylamine (3)	none	72	**2h**	no reaction
13	diphenylamine (1.1)	NEt_3 (2)	72	**2h**	no reaction
14	*N*-methylaniline (3)	none	72	**2i**	no reaction
15	*N*-methylaniline (1.1)	NEt_3 (2)	72	**2i**	no reaction
16	*N*-methylanisidine (1.1)	NEt_3 (2)	12	**2j**	66

[a] yields obtained for isolated products

The reaction could be extended to various secondary amines (entries 6-16), allowing the formation of 5-aminothiophene-2-carboxaldehydes **2** in high yields under simple reaction conditions (Table 1). The low yield obtained for compound **2g** (entry 11) can be explained by difficulties of removal of dibutylamine at the purification step. Reactions with diphenylamine and *N*-methylaniline (entries 12-15) did not lead to the desired aminothiophenes, probably due to the low nucleophilicity of these amines.

Using the more nucleophilic *N*-methyl *para*-anisidine, gave the *N*-[5-(4-methoxyphenyl)]-*N*-methylaminothiophene-2-carboxaldehyde **2j** in 66% yield. In comparison to other aminations by SNAr in the thiophene series[22-24], the higher yields which we describe here can be explained by a better solubilization and stabilization of the polar transition states in the water-amine mixture[27]. The actual role of water will be further investigated in an ongoing mechanistic study. The selectivity of the reaction with secondary amine was shown by reacting under the same

conditions a primary amine which only led to the formation of the imine **3** (Scheme 1).

In summary, we succeeded in the preparation of several *N,N*-disubstituted 5-aminothiophene-2-carboxaldehydes in high yield, one pot process using water as a solvent[28]. Selectivity of primary towards secondary amines has also been shown.

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28) Typical procedure for the SNAr of **1** with secondary amines in water: to **1** (0.38g, 2 mmol) and 4-hydroxy piperidine (0.6g, 6 mmol) were added 10ml of water. The resulting mixture was stirred overnight at reflux. The reaction flask was allowed to cool down to room temperature. The precipitate was filtrated and washed twice with water. The crude product was purified by chromatography on silica gel (CH_2Cl_2 / AcOEt 1:1) to furnish **2e**. **2e**: **m.p.** 142°C; **IR (KBr)** cm^{-1} : 1608. **UV/Vis (MeOH)** nm (ε): 371 (25200). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 1.72(m, 2H, C$\underline{H}_2$), 1.98(m, 2H, C$\underline{H}_2$), 2.65(brs, 1H, O$\underline{H}$), 3.21(m, 2H, C$\underline{H}_2$), 3.63 (m, 2H, C$\underline{H}_2$), 3.97 (m, 1H, C$\underline{H}$), 6.08 (d, 1H, H_4, J = 4.35Hz), 7.47 (d, 1H, H_3, J = 4.35Hz), 9.46 (s, 1H, CHO). **^{13}C NMR** ($CDCl_3$) δ 180.4 (CHO), 167.9 (C_5), 140.1 (C_3), 126.8 (C_2), 104.5 (C_4), 65.9 ($\underline{C}$HOH), 47.3 (N$\underline{C}H_2$), 32.8($\underline{C}H_2$). **Elemental analysis**: Calcd for $C_{10}H_{13}O_2NS$: C:56.85, H: 6.20, N: 6.63; Found: C: 56.97, H: 6.19, N: 6.81.