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A Facile Route to Unsymmetrical Sulfide

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Abstract: Unsymmetrical sulfides can be generated by the reaction of chlorine substituted aromatic compounds in sulfoxide in the presence of fluorine anion in fair yield. A likely mechanism was proposed.

Keywords: Unsymmetrical sulfide, aromatic nucleophilic substitution.

Unsymmetrical sulfides have been used extensively in pharmaceutical, agriculture and so forth. Many organic synthetic methods were employed to prepare the unsymmetrical sulfides successfully. For example, nucleophilic substitution of the thiolate on the alkyl halide[1], addition of thiophenol to alkene in the presence of AIBN as a catalyst[2], electrophilic substitution of dialkyldisulfide on the aromatic ring[3]. Herein, we report a simple procedure for preparing unsymmetrical sulfide based on the nucleophilic aromatic substitution.

Usually fluorine substituted aromatic compounds were prepared by the halogen exchange fluorination on the aromatic ring, called as $S_{Ar}2$ reaction. The chlorine substituted compound was used as the substrate, fluorine anion as the nucleophile, ammonium salt or crown ether as the catalyst. The reaction was carried out in the aprotic polar solvent, such as DMF, DMSO or HMPA. When relative high reaction temperature was involved, phosphonium salt and sulfolane were used instead of the ammonium salt, because the later easily decompose at high temperature. For example, 2, 6-difluorobenzonitrile was prepared in excellent yield by this method[4].

However, when we treated the *p*-chlorobenzaldehyde with potassium fluoride in dimethylsulfoxide at 180°C, *p*-meththiobenzaldehyde was detected by GC-MS. Methyl sulfide and methyl sulfone were also detected. Using the column chromatography, *p*-meththiobenzaldehyde was isolated in 30% yield. In order to investigate the possiblemechanism, phenyl methyl sulfoxide was used instead of the dimethylsulfoxide, the main product is 4-formyl diphenyl sulfide, which was isolated by column chromatography in 54% yield. The intermediate, such as thioanisole and methyl phenyl sulfone were also detected by GC-MS. In order to further support the mechanism, thioanisole, being suggested as intermediate, was used as reaction substance in the sulfolane, and 4-formyl diphenyl sulfide was prepared too. The likely mechanism was

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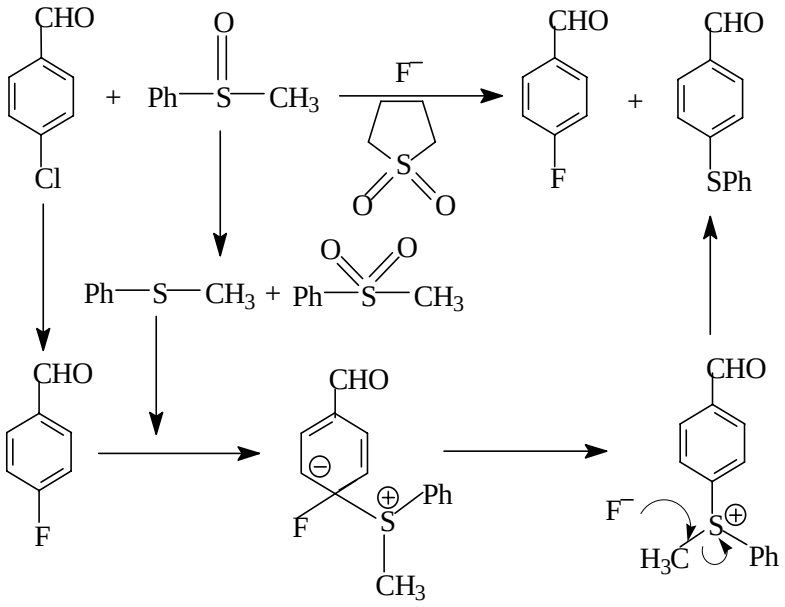
shown in **Figure 1**. The key intermediate is the carbanion, which could not be formed when the reaction ran without the participation of the fluorine anion. This is probably due to the strong electron withdrawing effect of the fluorine stabilizing intermediate. Moreover, from isolation and identification of this by-product, we know that fluorination of chlorobenzaldehyde should be carried out in the sulfolane solvent instead of the dimethylsuloxide when the high temperature was employed.

Figure 1 Proposed mechanism of the formation of unsymmetrical sulfide



Experiments and Results

4-Chlorobenzaldehyde, 4-chlorobenzonitrile, phenyl methyl sulfoxide and sulfolane were purchased from Aldrich. 4-Chloronitrobenzene was purchased from Shanghai No.1 Reagent Factory. 2,4-Dichlorobenzaldehyde was prepared according to reference[5]. Spray dried potassium fluoride was obtained from Dongyang Chemical Co.. Mp was recorded on Buchi 535. GC-MS was recorded on HP6890GC-5973MSD. Proton NMR was recorded on Bruker 400MHz.

A mixture of substrate (0.01 mol), dimethyl sulfoxide (1.56 mL, 0.022 mol), sulfolane (5.7 mL, 0.06 mol) and potassium fluoride (0.087 g, 0.0015 mol) were placed in a three-neck round-bottom flask equipped with a reflux condenser and a thermometer. The mixture was stirred at 180°C and monitered by gas chromatography (column: OV-17). After reaction, the reaction mixture was extracted by ether. The organic

phase was washed with water for another two times. After concentration, the residue was isolated by column chromatography. The results were listed in **Table1**.

Table 1 Characterization of the products

Substrate[a]	Product[b] (Yield/%)	mp/°C	δ H in ppm	IR(KBr)/cm^{-1}	MS (M^+)
1	A(10)	63-66	8.13 (d, 2H, J=8Hz), 7.29 (d, 2H, J=8Hz), 2.56 (s,3H)	2999,1584,1508, 1477,1337	169
2	B (35)	58-61	7.53 (d, 2H, J=8Hz), 7.26 (d, 2H, J=8Hz), 2.51 (s,3H)	2926,2223,1596, 1485,1237	149
3	C (30)	liq	9.91 (s, 1H), 7.76 (d, 2H, J=7Hz), 7.36 (d, 2H, J=7Hz), 2.53 (s, 3H)	2983,1708,1594, 1375,1248	152
3[c]	D(54)	52-54	9.87 (s ,1H), 7.61 (d, 2H, J =7 Hz), 7.39 (d, 2H, J=7 Hz), 7.20 (d, 2H, J=7.5 Hz), 7.02 (m, 3H)	3010,1695,1590, 1575,1388	184
4	E(71)[d]	52-58[e]	10.36 (s,1H), 7.81(d,1H, J=8Hz), 7.21(s,1H), 7.17 (d,1H,J=8Hz), 2.53 (s,3H) 10.18 (s, 1H), 7.73 (d, 1H, J=8Hz), 7.27 (s,1H), 7.24 (d,1H,J=8Hz), 2.50 (s,3H)	2866,1685,1582, 1541,1473,1260, 1231	186

a: 1: 4-chloronitrobenzene 2: 4-chlorobenzonitrile
3: 4-chlorobenzaldehyde 4: 2,4-dichlorobenzaldehyde;
b: A: Methyl 4-nitrophenyl sulfide B: 4-methylthiobenzonitrile
C: 4-methylthiobenzaldehyde D: 4-formyl diphenyl sulfide
E: 2-chloro-4-methylthiobenzaldehyde and 4-chloro-2-methylthiobenzaldehyde;
c: The reaction was carried out in phenyl methyl sulfoxide;
d: 2-chloro-4-methylthiobenzaldehyde: 4-chloro-2-methylthiobenzaldehyde =1.6:1;
e: The mp(°C) refers a 1.6:1 mixture of isomers.

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