Superelectrophilic Methylthiomethylation of Aromatics with Chloromethyl Methyl Sulfide/Aluminum Chloride ($MeSCH_2Cl:2AlCl_3$) Reagent[1]

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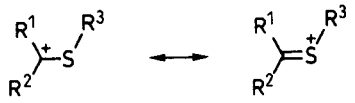
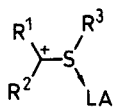
Effective methylthiomethylation of aromatics was achieved by using chloromethyl methyl sulfide/aluminum chloride ($MeSCH_2Cl:2AlCl_3$) as the alkylating agent. Excess aluminum chloride activates the thiocarboxonium ion intermediate by coordinating with sulfur and thus diminishes back donation of "electron density" into the carbocationic center, rendering it a superelectrophilic methylthiomethylating agent.

Alkylthioalkylation of aromatics is a useful reaction because the products can be readily further transformed into other functionalities.[2] The application of the reaction is, however, severely limited since the reaction generally only works well with phenolic substrates.[2,3] Although progress has been made in expanding the scope of the reaction,[4] developing convenient procedures and reagents for alkylthioalkylation of aromatics is still desirable.

As thiocarboxonium ions are the expected reaction intermediates of the alkylthioalkylation, the low reactivity of the reaction most likely results from the stabilization of the carbocationic center by the adjacent sulfur atom.



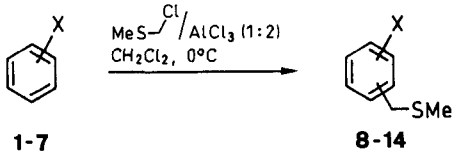
Our previous work on 2,2,2-trifluoro-1-(ethylthio)ethylation of arenes supports this suggestion.[4a] Attaching a strongly electron withdrawing CF_3-group to the adjacent carbocation center enhanced the reactivity of the thiocarboxonium ions and extended the scope of alkylthioalkylation to reactive arenes such as benzene and toluene. One way to increase the electrophilicity of the carbocationic species is to reduce the electron donating ability of the adjacent sulfur atom by Lewis acid complexation. This so called electrophilic solvation of thiocarboxonium ions enhances their carbocationic reactivities and thus renders them superelectrophiles. It has been previously shown that electrophilic solvation enhanced such diverse reactions as nitration, iodination, and amidoalkylation.[5,6]



Gross and Matthey reported that chloromethyl methyl sulfide was not an effective agent for methylthiomethylation of aromatics using one molar equivalent of titanium(IV) chloride.[7] Toluene was alkylated in only 37% yield. In view of our continuing interest in the alkylthioalkylation[4a] and electrophilic solvation,[5,6] we decided to reinvestigate the methylthiomethylation with chloromethyl methyl sulfide as reagent, but using excess Lewis acid, and we report our results herein.

Aluminum chloride was used as the Friedel–Crafts Lewis acid in our study. When 1 molar equivalent of aluminum chloride was slowly added to a mixture of chlorobenzene and chloromethyl methyl sulfide (1:1 molar ratio) in anhydrous dichloromethane at 0 °C, reaction took place immediately with evolution of hydrogen chloride. After 2 hours, a 58% yield of thioalkylated chlorobenzene was obtained. By adding 1 equivalent of chloromethyl methyl sulfide to a 1:1 mixture of chlorobenzene and aluminum chloride, alkylated products were obtained after 2 hours in 77%. However, by adding chloromethyl methyl sulfide to a 1:2 mixture of chlorobenzene and aluminum chloride at 0 °C, chlorobenzene was nearly quantitatively converted into the methylthiomethylation products in only 30 minutes.

The isolated product consists of a mixture of *ortho*- and *para*-isomers (15:85) with no detectable amount of *meta*-isomer (Tables 1 and 2).



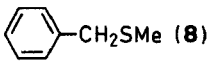
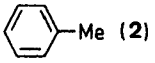
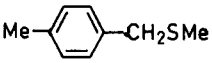
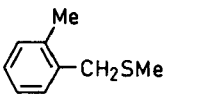
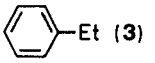
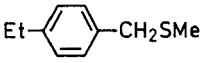
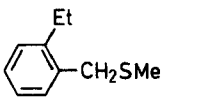
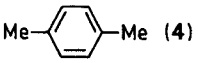
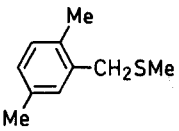
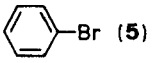
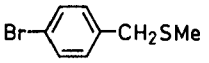
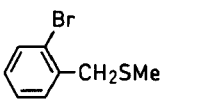
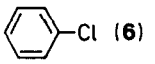
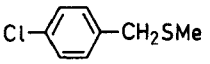
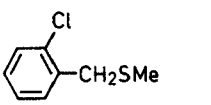
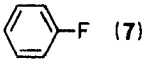
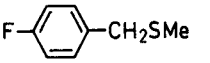
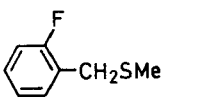
1-7 **8-14**

Both the results of reverse addition with 1 equivalent of aluminum chloride and the use of 2 molar equivalents of aluminum chloride demonstrate the effect of using excess Lewis acid in the reaction. When aluminum chloride and chloromethyl methyl sulfide, were mixed in a 1:1 molar ratio in chloroform-*d*, we only observed a broad methylene peak in ^{13}CNMR at δ = 48.3. With the ratio increasing to 2:1, a second methylene peak downfield from the first by 4.5 ppm appeared, which indicates further coordination of aluminum chloride with chloromethyl methyl sulfide.

Benzene, toluene, ethylbenzene, *p*-xylene as well as fluoro-, and bromobenzene were also effectively methylthiomethylated under the same reaction conditions (Table 1). The reaction, however, did not proceed with benzophenone and nitroarenes. Those reactions failed even under refluxing conditions and after increasing the aluminum chloride ratio to 3:1. In these cases, it is assumed that coordination of the oxygen atom(s) of the substrates with the Lewis acid competes with *S*-coordination, which renders the alkylation of the deactivated aromatics ineffective.

In conclusion, we have found that the alkylating ability of chloromethyl methyl sulfide toward aromatics is greatly enhanced by using excess Lewis acid. Further coordination of the intermediate thiocarboxonium ion explains the increased reactivity in the reaction. Attention is called to the fact that the use of excess Lewis acid in Frie-

Table 1. Methylthiomethylation of Aromatics with $MeSCH_2Cl$: $2AlCl_3$

Substrate	Products[a]	Yield (%)	bp (°C)/Torr found	bp (°C)/Torr reported
 (1)	 (8)	87	70–72/4	98–100/12[7]
 (2)	 (9a) +  (9b) (82 : 18)	83	86–86/4	81–83/1[7]
 (3)	 (10a) +  (10b) (83 : 17)	86	89–91/4	–[b]
 (4)	 (11)	94	72–74/3	–[b]
 (5)	 (12a) +  (12b) (76 : 24)	76	105–107/1	–[c]
 (6)	 (13a) +  (13b) (85 : 15)	92	76–77/2	–[c]
 (7)	 (14a) +  (14b) (93 : 7)[e]	82	50–51/4	–[d]

[a] Isomer ratios were determined by ^1H NMR spectroscopy. The amount of meta isomers could not be determined by NMR as they are low (< 3%) in all cases. The major product of the reaction was identified in all eases by spectroscopic data which were in accordance with their structures and is a literature known compound.

[b] Not reported in Ref. 4d.

[c] Not reported in Ref. 4e.

[d] Not reported in Ref. 8.

[e] Determined by ^{19}F NMR spectroscopy.

Table 2. Spectroscopical Data of Pure para-Isomers **8–14a** Prepared

Product	^{1}H NMR ($CDCl_3$/TMS) δ	^{13}C NMR ($CDCl_3$/TMS) δ	MS (M^+) m/z (%)
8	2.0 (s, 3H), 3.66 (s, 2H), 7.29 (m, 5H)	14.8, 38.2, 126.8, 128.4, 128.8, 138.2	138 (40)
9a	1.97 (s, 3H), 2.32 (s, 3H), 3.63 (s, 2H), 7.11 (d, 2H, J = 8.2), 7.18 (d, 2H, J = 8.2)	14.8, 21.0, 37.9, 128.8, 129.1, 135.1, 136.4	152 (36)
10a	1.22 (t, 3H, J = 7.6), 2.0 (s, 3H), 2.63 (q, 2H, J = 7.6), 3.64 (s, 2H), 7.14 (d, 2H), J = 8.2), 7.21 (d, 2H, J = 8.2)	14.9, 15.5, 28.4, 38.0, 127.9, 128.7, 135.3, 142.9	166 (35)
11	2.02 (s, 3H), 2.29 (s, 3H), 2.33 (s, 3H), 3.63 (s, 2H), 6.96 (d, 1H, J = 7.8), 6.98 (s, 1H), 7.05 (d, 1H, J = 7.8)	15.1, 18.6, 20.8, 36.2, 127.8, 130.3, 130.4, 133.3, 135.0, 135.6	166 (35)
12a	1.97 (s, 3H), 3.61 (s, 2H), 7.17 (d, 2H, J = 8.4), 7.43 (d, 2H, J = 8.4)	14.8, 37.6, 120.6, 130.5, 131.5, 137.2	218 (34), 216 (35)
13a	1.97 (s, 3H), 3.62 (s, 2H), 7.22 (d, 2H, J = 8), 7.28 (d, 2H, J = 8)	14.8, 37.6, 128.5, 130.1, 132.6, 136.7	174 (11), 172 (32)
14a[a]	1.97 (s, 3H), 3.64 (s, 2H), 6.99 (t, 2H, $^3J_{H,H} = {}^3J_{H,F}$ = 8.7), 7.26 (dd, 2H, $^3J_{H,H}$ = 8.7, $^3J_{H,F}$ = 5.4)	14.8, 37.5, 115.2 (d, $^2J_{C,F}$ = 22), 130.3 (d, $^3J_{C,f}$ = 8.3), 133.9 (d, $^4J_{C,F}$ = 3.2), 161.8 (d, $^1J_{C,F}$ = 245)	156 (26)

[a] ^{19}F NMR ($CFCl_3$): δ = −116 (m)

del–Crafts reactions greatly enhances the reactivity of reagents that are capable of further coordination thus rendering them superelectrophilic in nature.

All chemicals used were purchased from Aldrich. NMR spectra were obtained on a Varian Associate Model VXR-200. MS analyses were performed on a Hewlett Packard 5971 Mass Spectrometer (EI).

Methylthiomethylation of Aromatics; Typical Procedure:
To a stirred mixture of $AlCl_3$ (2.7 g, 20 mmol) and the corresponding arene (10.2 mmol) was added chloromethyl methyl sulfide (1.01 g, 95%, 10 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was quenched with ice, and extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were washed sequentially with H_2O, aq $NaHCO_3$, brine, and dried ($CaCl_2$). After filtration and evaporation of the solvent, the products were obtained by distillation (Table 1.).

We thank the National Science Foundation and the National Institutes of Health for financial support.

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(b) Olah, G. A.; Laali, K. K.; Sandford, G. *Proc. Natl. Acad. Sci. USA.* **1992**, *89*, 6670.
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