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LETTERS

Electrochemical Electrophilic Aromatic Methylthiation in Liquid SO_2

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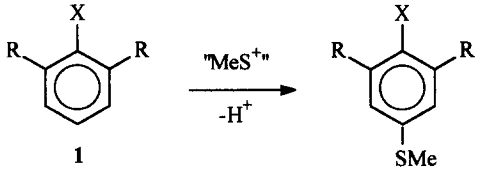
Abstract: Controlled potential electrolysis of dimethyldisulfide in liquid sulfur dioxide provides a strongly electrophilic methylthiating agent. This species methylthiates strongly to weakly activated arenes in good to excellent yield. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Disulfide, electrochemistry, electrophilic aromatic substitution, sulfur dioxide

Electrophilic aromatic thiation is typically accomplished by the use of a sulfenyl chloride,[2] disulfide,[3] or thiosulfonate[4] and a Lewis or Bronsted acid, although acid catalysis is not necessary for the reaction of phenols or dialkylamino-4-hydroxypyrimidines[5] with sulfenyl chlorides and sulfenylation occurs with methane- or arenesulfenyl chlorides and pyridines with 3-t-butyl-6-methylsalicylic acid.[6] 1-Substituted pyrroles and indoles undergo methylthiation with methanesulfenyl chloride and pyridine or with 1-methylthiomorpholine and trifluoroacetic acid.[7] Silica gel[8] and zeolites[9] have also been used to catalyze the reactions of sulfenyl chlorides with arenes and Me_2S_2 with phenol, respectively. Intramolecular versions of aromatic thiation are also known.[10] Recently, a method was reported[11] for accomplishing this reaction using sulfenium ions, RS^+, electrochemically generated from disulfides. Thus controlled potential electrolysis of Me_2S_2 in CH_2Cl_2 followed by addition to phenols and anisoles afforded the corresponding methylthio derivatives in 26-77 and 11-35% yields (combining the yields of regiosomers if formed), respectively as outlined in eq. 1.



1 2 (1)

It has been reported[12] that liquid SO_2 is an excellent electrochemical solvent and highly reactive aromatic mono- and polycations can be reversibly produced in this solvent. Furthermore, the chemical preparation in liquid SO_2 of a methylthiating agent: $(MeS)_2SMe^+$, has been reported[13] and this species is stable in this solvent. Consequently, the electrochemical oxidation of dimethyldisulfide in liquid SO_2 and use of this oxidized product for methylthiation of aromatic compounds has been investigated.

Cyclic voltammetric studies on Me_2S_2 in liquid SO_2, 0.1 M in n-Bu_4NBF_4, at a scan rate of 0.1 V/s have been carried out. An electrochemically irreversible two-electron oxidation with $E_p = 1.15$ V, a quasi-reversible one-electron oxidation at *ca.* 3.0 V and an irreversible oxidation at *ca.* 3.5 V vs Ag wire are observed. Controlled potential electrolysis of Me_2S_2 in liquid SO_2 at the potential of the irreversible two-electron oxidation generates a methylthiating species. Addition of an aromatic compound to this species results in methylthiation as shown in eq. 1 in the yields reported in the Table, which are based on consumed arene of which 50 – 65% is typically consumed. This represents a significant improvement in the method previously reported using CH_2Cl_2 as solvent. The procedure used is as follows. A two-compartment electrochemical cell divided by a sintered glass diaphragm was used. A solution of Me_2S_2 (3 mmol) in liquid SO_2 (25 ml) maintained at – 45 to –30°C, 0.1 M in n-Bu_4NPF_6 was electrolyzed using a cylindrical Pt gauze electrode (40 mm length, 12 mm diam.) as anode at a potential of 0.6-2.0 V vs Ag wire until the amount of electricity passed was equivalent to 2F/mol. The cathode was Al foil (70 x 100 mm). After completion of the electrolysis the oxidized solution was siphoned into a cooled flask containing the arene (3 mmol). After stirring at – 15°C for 3 hr. the SO_2 was allowed to evaporate, CH_2Cl_2 (10 ml) added, followed by Et_2O (25 ml) to precipitate the n-Bu_4NPF_6, and the organic layer separated. The solvents were removed by evaporation and the product analyzed by GC and, in some cases, isolated by column chromatography on silica gel.

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As can be seen in the Table, a large range of activated as well as weakly activated arenes are methylthiated in good to excellent yields. The yields of methylthiation of phenols and phenyl ethers are much higher using this method than in using the previously reported[11] electrochemical method. Furthermore, the reaction is regioselective providing the *p*-methylthiated product preferentially except for 3,5-dimethylphenol, in which case the *o*-methylthiated product is selectively formed. Polymethylthiation is observed and, in the case of thiophene, the bis-methylthiated product is formed predominantly under these conditions. Of course with greater amounts of methylthiation agent, polymethylthiation is favored. Thus doubling the amount of methylthiating agent results in the conversion of phenol into its bis-methylthiated product and a small amount of its tris-methylthiated product in excellent yield.

In sum, a strongly electrophilic methylthiating agent is formed on controlled potential electrolysis of Me_2S_2 in liquid SO_2 which methylthiates a wide range of arenes in good to excellent yield.

Table. Methylthiation of Arenes in Liquid SO_2

Arene	**Product**	**Yield**^{a}
PhOH	o-$MeSC_6H_4OH$	9.5^b
	p-$MeSC_6H_4OH$	83^b
3,5-$(Me)_2C_6H_3OH$	2-(MeS)-3,5-$(Me)_2C_6H_2OH$	99^b
1, X = OH, R = Me	**2**, X = OH, R = Me	97^b, 81^c
PhOMe	p-$MeSC_6H_4OMe$	82^b
PhOPh	p-$MeSC_6H_4OPh$	49^c
	$(p$-$MeSC_6H_4)_2O$	9^c
1, X = R = OMe	**2**, X = R = OMe	53^b
PhSMe	p-$MeSC_6H_4SMe$	68^c
1, 4-$(Me)_2C_6H_4$	2-(MeS)-1,4-$(Me)_2C_6H_3$	60^b
	2,5-$(MeS)_2$-1,4-$(Me)_2C_6H_2$	26^b
anthracene	9-(MeS)anthracene	78^c
thiophene	2,5-$(MeS)_2$ thiophene	57^c

^{a} % yields are based on consumed arene, ^{b} GC yield, ^{c} Isolated yield

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