

Electrochemical Electrophilic Aromatic Methylthiation in Liquid SO₂

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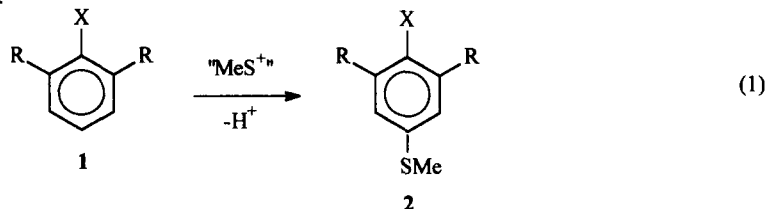
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Abstract: Controlled potential electrolysis of dimethyldisulfide in liquid sulfur dioxide provides a strongly electrophilic methylthiating agent. This species methylthiates strongly to weakly activated arenes in good to excellent yield. © 1999 Elsevier 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 thiosulfonate⁴ and a Lewis or Bronsted acid, although acid catalysis is not necessary for the reaction of phenols or dialkylamino-4-hydroxypyrimidines⁵ 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 gel⁸ and zeolites⁹ have also been used to catalyze the reactions of sulfenyl chlorides with arenes and Me₂S₂ with phenol, respectively. Intramolecular versions of aromatic thiation are also known.¹⁰ Recently, a method was reported¹¹ for accomplishing this reaction using sulfenium ions, RS⁺, electrochemically generated from disulfides. Thus controlled potential electrolysis of Me₂S₂ in CH₂Cl₂ 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.



It has been reported¹² that liquid SO₂ 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 SO₂ of a methylthiating agent: (MeS)₂SMe⁺, has been reported¹³ and this species is stable in this solvent. Consequently, the electrochemical oxidation of dimethyldisulfide in liquid SO₂ and use of this oxidized product for methylthiation of aromatic compounds has been investigated.

Cyclic voltammetric studies on Me₂S₂ in liquid SO₂, 0.1 M in *n*-Bu₄NBF₄, 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 Me₂S₂ in liquid SO₂ 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 CH₂Cl₂ as solvent. The procedure used is as follows. A two-compartment electrochemical cell divided by a sintered glass diaphragm was used. A solution of Me₂S₂ (3 mmol) in liquid SO₂ (25 ml) maintained at –45 to –30°C, 0.1 M in *n*-Bu₄NPF₆ 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 SO₂ was allowed to evaporate, CH₂Cl₂ (10 ml) added, followed by Et₂O (25 ml) to precipitate the *n*-Bu₄NPF₆, 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.

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 reported¹¹ 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 Me₂S₂ in liquid SO₂ which methylthiates a wide range of arenes in good to excellent yield.

Table. Methylthiation of Arenes in Liquid SO₂

Arene	Product	Yield ^a	Arene	Product	Yield ^a
PhOH	<i>o</i> -MeSC ₆ H ₄ OH	9.5 ^b	1, X = R = OMe	2, X = R = OMe	53 ^b
	<i>p</i> -MeSC ₆ H ₄ OH	83 ^b	PhSMe	<i>p</i> -MeSC ₆ H ₄ SMe	68 ^c
3,5-(Me) ₂ C ₆ H ₃ OH	2-(MeS)-3,5-(Me) ₂ C ₆ H ₂ OH	99 ^b	1, 4-(Me) ₂ C ₆ H ₄	2-(MeS)-1,4-(Me) ₂ C ₆ H ₃	60 ^b
1, X = OH, R = Me	2, X = OH, R = Me	97 ^b , 81 ^c		2,5-(MeS) ₂ -1,4-(Me) ₂ C ₆ H ₂	26 ^b
PhOMe	<i>p</i> -MeSC ₆ H ₄ OMe	82 ^b	anthracene	9-(MeS)anthracene	78 ^c
PhOPh	<i>p</i> -MeSC ₆ H ₄ OPh	49 ^c	thiophene	2,5-(MeS) ₂ thiophene	57 ^c
	(<i>p</i> -MeSC ₆ H ₄) ₂ O	9 ^c			

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

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