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EFFICIENT SYNTHESIS OF ARYL METHYL SULFIDE DERIVATIVES USING (METHYLTHIO)TRIMETHYLSILANE AS METHYLTHIOLATION REAGENT

Qi Qiao, Romyr Dominique, Achyutharao Sidduri, Jianping Lou, and Robert A. Goodnow, Jr.
Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey, USA

The synthesis of various aryl methyl sulfides has been achieved by treatment of nitroarenes with a combination of (methylthio)trimethylsilane and cesium carbonate in dimethylsulfoxide. This reaction gives access to aryl methyl sulfide derivatives in high yields.

Keywords: Aryl methyl sulfides; methylthiolation; (methylthio)trimethylsilane; nitroarenes; nucleophilic displacement

Aryl methyl sulfides and aryl methyl sulfones are found in many pharmaceutically important molecules.[1] Consequently, they are frequently incorporated as building blocks in structure-activity relationship (SAR) development of medicinal entities. Several synthetic methods have been reported for the formation of aryl-sulfur bonds. The most common methods include lithium exchange of aryl halides and subsequent quenching with an alkyldisulfide or elemental sulfur,[2] metal-catalyzed (Cu, Ni, Pd) cross-coupling reactions of aryl halides and triflates with sulfides or sulfinic acid salts[3] and substitution reactions of thiolate anions on activated aryl halides.[4] However, these reactions are often not compatible with substrates having sensitive functional groups.

During the course of our SAR exploration, we were interested in preparing aryl methyl sulfide and aryl methylsulfone derivatives. Oshima et al.[5] recently reported the nucleophilic aromatic substitution reaction (S_NAr) of nitroarenes bearing strong electron-withdrawing groups (EWG) with alkyl and aryl thiols under the mediation of cesium carbonate. However, the use of methanethiol has not been reported to date, perhaps due to practical handling considerations (e.g., methanethiol is a toxic, malodorous gas at room temperature). We envisioned that such a method could be adapted for the preparation of various aryl methyl sulfide derivatives if a non-volatile chemical equivalent of methanethiol could be identified. We anticipated that

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Address correspondence to Dr. Romyr Dominique, Roche Research Center, 340 Kingsland Street, Nutley, NJ 07110, USA. E-mail: romyr.dominique@roche.com

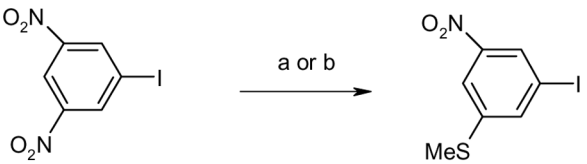
Scheme 1. General method for the preparation of aryl methyl sulfide derivatives.

commercially available (methylthio)trimethylsilane (TMSSMe)[6] would generate methanethiolate *in situ* when treated with a base (Scheme 1).

TMSSMe has been previously reported in literature as a reagent for thioketalization[7] reactions, methyl ether cleavage,[8a] preparation of thioesters,[8b] preparation of methylthio-substituted sugars[8c] and also for the preparation of aryl methyl sulfide by the reaction with arenediazonium tetrafluoroborates.[9] In the last case, this methodology was reported only with arenediazonium salts thus it would be advantageous to be able to perform the same type of transformation by direct replacement of aromatic nitro groups which are known to be common precursors to arenediazonium salts through aniline derivatives, thereby, reducing the number of steps in a synthetic scheme. To the best of our knowledge, TMSSMe has never been reported as methylthiolation reagent for the nucleophilic displacement of aromatic nitro groups. Herein, we report an efficient and convenient method which uses the combination of TMSSMe and Cs_2CO_3 in DMSO as a methylthiolation reagent for the preparation of aryl methyl sulfide derivatives; the scope of the reaction is also described.

In order to investigate the utility of this new methodology, we set out to compare the substitution reactions of 1-iodo-3,5-dinitrobenzene with sodium thiomethoxide (NaSMe), which has often been reported to perform the same type of nucleophilic displacement on nitroarenes.[10] However, in our hands, the reaction with NaSMe gave unsatisfactory results, resulting in decomposition or lower yields depending on the amount of NaSMe used. On the other hand, performing the same reaction with TMSSMe gave an excellent yield when 1.4 equiv. of TMSSMe and 1.6 equiv. of cesium carbonate were used. Under these conditions, 1-iodo-3-methylsulfanyl-5-nitro-benzene (**2**) was obtained in 97% yield (Scheme 2).

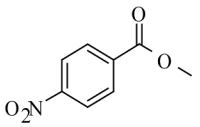
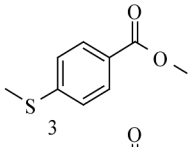
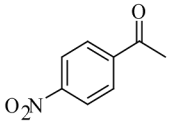
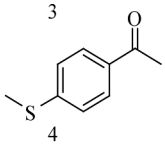
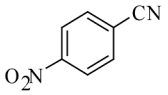
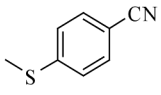
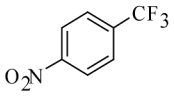
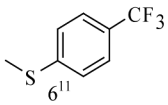
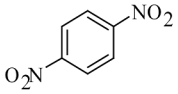
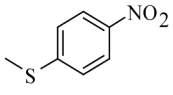
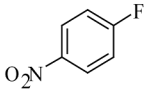
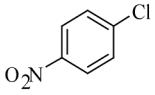
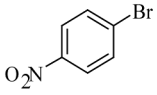
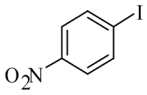
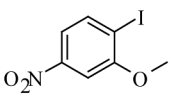
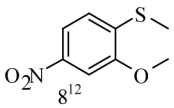
Once the best conditions were established, a variety of aryl methyl sulfide derivatives were synthesized in good to excellent yields from commercially available nitroarenes. The mild reaction conditions are compatible with diverse functional groups such as esters, cyanides and methyl ketones as shown in Table 1 (e.g., entries



1 **2**

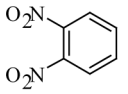
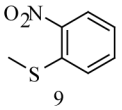
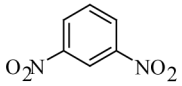
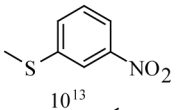
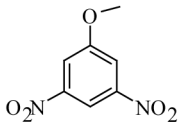
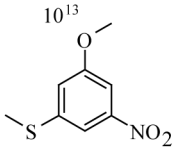
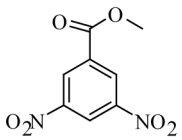
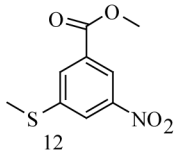
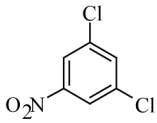
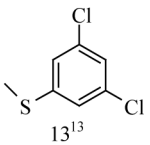
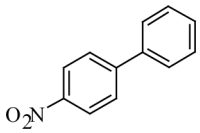
Scheme 2. a) NaSMe, DMSO, r.t., 16 h; b) TMSSMe, Cs_2CO_3, DMSO, r.t., 16 h.

Table 1. Results for the reaction of nitroarenes with $TMSSMe/Cs_2CO_3$

Entry	Nitroarene	Aryl methyl sulfide	Yield (%)[a]
1		 3	88
2		 4	89
3		 5	92
4		 6[11]	76
5		 7	98
6		7	96
7		7	97
8		7	78
9		7	60
10		 8[12]	81

(*Continued*)

Table 1. Continued

Entry	Nitroarene	Aryl methyl sulfide	Yield (%)[a]
11		 9	93
12		 10[13]	20[b]
13		 11	27
14		 12	20[c]
15		 13[13]	83
16		—	No Reaction

[a]Isolated yield after column chromatography.
[b]77 % of starting material was recovered.
[c]55% of starting material was recovered.

1, 2, 3, and 14). As anticipated, it was also found that the best yields were obtained for substrates containing an electron-withdrawing group in the *ortho* or *para* position on nitroarenes. The presence of an electron-withdrawing group at those positions activates the nitro group and increase its propensity for displacement. The reaction of 1,2-dinitrobenzene proceeds almost quantitatively (e.g., entry 11). All other electron-withdrawing substituted phenyl substrates such as those *para*-substituted with esters, ketones, trifluoromethyl and nitro groups underwent nucleophilic displacement with good to excellent yields (Table 1, entries 1–5). With 4-nitrobiphenyl no reaction was observed, probably due to the fact that the phenyl moiety did not activate the nitro group sufficiently for the nucleophilic displacement to occur (entry 16). All *para*-halonitrobenzenes provided the unanticipated *para*-methylthionitrobenzenes (**7**) where the halogen atom was displaced by the

methanethiolate anion while leaving the nitro group in place (e.g., entries 6–9). The identification of (**7**) was also confirmed by observing that the reaction with 1,4-dinitrobenzene and TMSSMe afforded an identical product. We rationalized that the displacement of the halogen substituent could perhaps be favored since the halogen substituent was activated by the stronger electron-withdrawing capacity and charge stabilizing effect of the nitro group, thus displaced exclusively by TMSSMe.

To expand the scope of this methodology, we explored the nucleophilic displacement of the nitro group on disubstitued nitroarenes. It is worth to mention that the presence of an *ortho*-methoxy group did not impede the replacement of the activated iodide located in the *para* position with respect to the nitro group (entry 10). All *meta* substituted nitrobenzenes proceeded in poor yield under the same conditions (Table 1, entries 12–14). However, the disubstituted nitroarenes in Entry 15 and the example shown in Scheme 2 produced the desired aryl methyl sulfides in high yields. In those examples, the halogen is located on the meta-position and is not activated, and only the nitro group is displaced, giving access to interesting disubstituted aryl methyl sulfide derivatives.At this time, the mechanism of this reaction is not fully understood. Although, we could believe that the reaction proceeds through a nucleophilic aromatic substitution,[5] some of our results such as the formation of compound **2** might be better rationalized by radical anion chemistry through a single electron transer (SET) mechanism. Further work would be needed to investigate the mechanism of this reaction.

In summary, the combination of (methylthio)trimethylsilane (TMSSMe) and Cs_2CO_3 in DMSO at room temperature was found to be efficient as a methylthiolation reagent in accomplishing the nucleophilic displacement of aromatic nitro groups. High chemical yields, combined with operationally convenient conditions, render this method practically useful for the preparation of aryl methyl sulfide derivatives.

EXPERIMENTAL

All chemicals and solvents were of commercial quality and used without further purification. Compounds were characterized either by ^{1}H-NMR using a Varian Inova 400 MHz NMR Spectrometer or a Varian Mercury 300 MHz NMR Spectrometer as well as by high resolution mass spectrometry using a Bruker Apex-II high-resolution 4.7 T FT-Mass Spectrometer. All products were purified by flash-column chromatography using pre-packed silica gel columns (RediSep) eluted with a CombiFlash system.

Representative Procedure for the Synthesis of Aryl Methyl Sulfides: Synthesis of 1-Iodo-3-methylsulfanyl-5-nitro-benzene (2)

To a solution of 1-iodo-3,5-dinitrobenzene (891 mg, 3.03 mmol) in DMSO (5 ml) was added Cs_2CO_3 (1.58 g, 4.84 mmol) and the mixture was stirred for 2 min. TMSSMe (0.6 ml, 4.23 mmol) was added to give a dark purple solution. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with water (25 ml) and extracted with EtOAc (50 ml). The organic layer

was washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide a solid as the crude product. Purification using flash column chromatography (10% EtOAc/Hexanes) afforded the compound as a yellow powder (868 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, s, Ph), 7.99 (1H, s, Ph), 7.81 (1H, s, Ph), 2.54 (3H, s, CH3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 143.6, 139.5, 128.2, 119.4, 93.5, 15.4. HR-MS m/z calcd. for $C_7H_6NO_2SI$: 294.9164; found: 294.9165.

4-Methylsulfanyl-benzoic Acid Methyl Ester (3)

^{1}H NMR (400 MHz, DMSO) δ: 7.85 (2H, m, Ph), 7.34 (2H, m, Ph), 3.81 (3H, s, OCH_3), 2.51 (3H, s, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 145.3, 129.7, 126.1, 124.7, 52.0, 14.8. HR-MS *m/z* calcd. For $C_9H_{10}O_2S$: 182.0402; found: 182.0402.

1-Methylsulfanyl-4-trifluoromethyl-benzene (6)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (2H, d, Ph), 7.30 (2H, d, Ph), 2.54 (3H, s, CH3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.7, 126.9, 126.5, 125.5, 122.9, 15.1. HR-EI m/z calcd. for $C_8H_7SF_3$: 192.0221; found: 192.0221.

2-Methoxy-1-methylsulfanyl-4-nitro-benzene (8)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (1H, d, Ph), 7.65 (1H, s, Ph), 7.11 (1H, d, Ph); 4.12 (3H, s, OMe); 2.51 (3H, s, CH3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.0, 146.2; 138.4; 122.3; 116.5; 104.8; 56.3; 15.6. HR-EI m/z calcd. for $C_8H_9NO_3S$: 199.0306; found: 199.0303.

1-Methylsulfanyl-2-nitro-benzene (9)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (1H, d, Ph), 7.60 (1H, t, Ph), 7.39 (1H, d, Ph), 7.23 (1H, t, Ph), 2.54 (3H, s, CH3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3, 139.2, 133.6, 126.1, 125.5, 124.1, 16.0. HR-EI m/z calcd. for $C_7H_7NO_2S$: 169.0198; found: 169.0197.

1-Methoxy-3-methylsulfanyl-5-nitro-benzene (11)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (1H, s, Ph), 7.47 (1H, s, Ph), 7.05 (1H, s, Ph), 3.88 (s, 3H, OMe), 2.54 (s, 3H, CH3). HR-EI m/z calcd. for $C_8H_9NO_3S$: 199.0294; found: 199.0303.

3-Methylsulfanyl-5-nitro-benzoic Acid Methyl Ester (12)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (1H, s, Ph), 8.20 (1H, s, Ph), 8.17 (1H, s, Ph), 3.98 (s, 3H, OMe), 2.60 (s, 3H, CH3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 148.5, 142.6, 131.9, 131.8, 123.6, 120.3, 52.9, 15.4. HR-MS m/z calcd. for $C_9H_9NO_4S$: 227.0252; found: 227.0252.

ACKNOWLEDGMENTS

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