

A New Method for Synthesis of Thioethers from Phenyl N-Sulfonamide

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Abstract: A operationally simple, one-pot for regioselective synthesis of thioether route directly from phenyl N-sulfonamide by using inexpensive, easily handled trimethylsilyl iodide as reducing agent, acetonitrile as the solvent is described. Further no catalyst or additive are required, which avoids contamination from the transition metal catalysts in the products.

Key words Trimethylsilyl iodide (TMS-I), Sulfonamide, Reductive dimerization, Regioselective, Thioethers.

Introduction:

The reactions forming carbon-sulfur bonds have received less attention, even though aryl thioethers are valuable synthetic intermediates frequently found in biologically and pharmaceutically active molecules. Indeed, several aromatic thioethers have shown potential clinical applications¹.

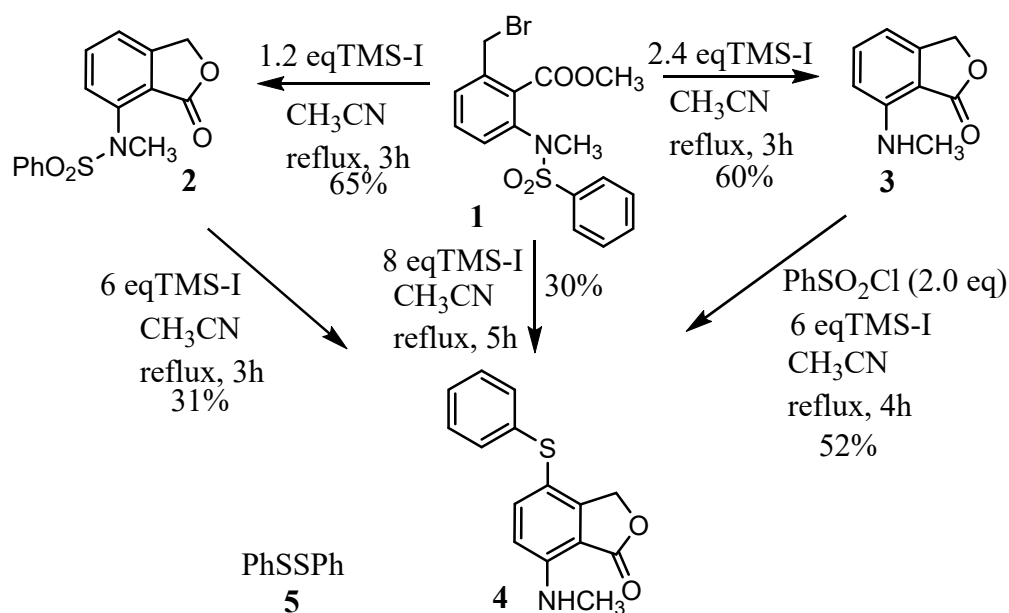
Past Work:

Among the numerous methods developed in the past decades, the most common and powerful approach are coupling of aniline with, thiol,² N-thio Succinimide³, Chloro with thiol⁴, iodo with thiol⁵, reductive methods such as sulfinic acid,⁶ Tosylhydrazine⁷ and disulfide⁸, thiol⁹ and rearrangement of sulfonamide in triflic acid¹⁰. Even though there are large reported methods for thioethers, there is always room for improvement and to find a novel and efficient method, especially were by using readily available, inexpensive, and easily handled reagent. Trimethylsilyl iodide (TMS-I) one such a versatile reagent, attracted our attention because It is well documented in the literature for the ester cleavage¹¹, and desulfonation¹² of amide are few well known methods.

Present Work:

In continuation of our ongoing work for the synthesis of 7-Aminomethyl phthalides based fluorescent for the study of Cysteine-Specific Blue Fluorescence Probe¹³, we developed a novel method for the synthesis of thioether **4** by a one-pot reaction by using the commercial available, trimethylsilyl iodide as a reagent in acetonitrile under reflux conditions, where it undergo multiple functional group changes, varies with mole equivalent of TMS-I used in the reaction

scheme-1



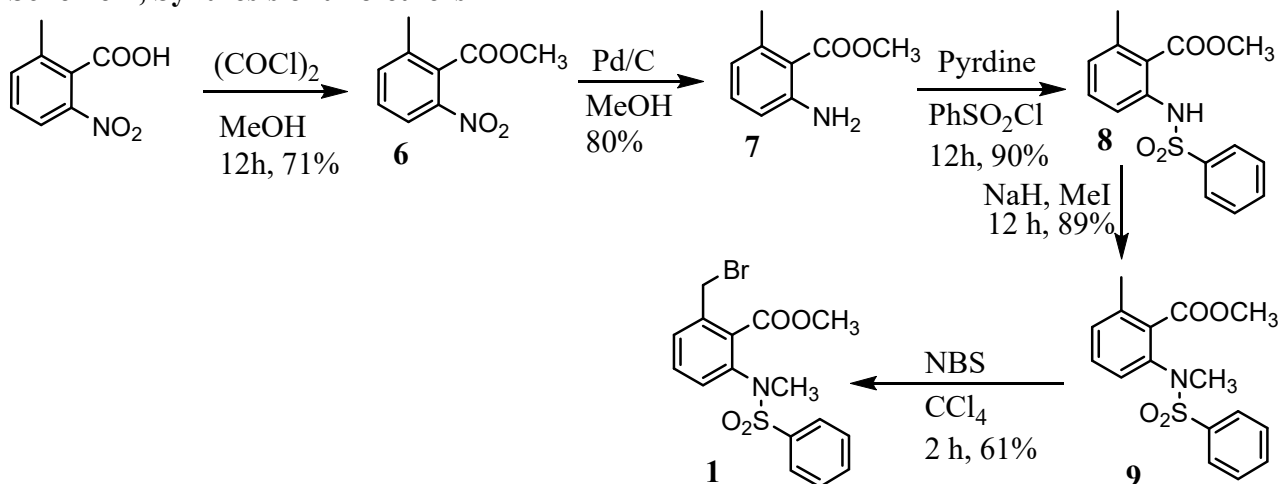
Scheme-1: When we treated substrate having trifunctional groups, **1** with 1.2 equivalent of TMS-I gives the Phthalimide-7-N-sulfonamide **2** by ester cleavage. In another reaction, the compound **1** on treatment with 2.4 eq of TMS-I, initially formed Phthalimide-7-N-sulfonamide **2** further undergoes desulfonation gives the phthalide-7-methylamine **3**. As reported in the literature where TMS-I is used for reductive dimerization of phenyl sulfinic acid sodium salt or phenyl sulfonyl chloride to form the disulfide¹¹ which go through phenyl sulfenyl radical mechanism. To test whether it is possible to trap the *in situ* generated phenyl sulfenyl radical by phthalimide-7-methylamine **3** in one pot reaction, we carried a reaction by treating the substrate **1** with excess (8 eq) of TMSI, to generate phenyl sulfenyl radical after desulfonation. Surprisingly, it gives regio selective product, thioether **4** by C-S bond formation in 30% yield. The yield is low due to competitiveness between the phenyl sulfenyl radicals (to form dimer) and its reaction with phthalide-7-methylamine **3** to form thioether **4**. Independently thioether **4** is obtained treating by 6 equivalents of TMS-I with phthalimide-7-N-sulfonamide **2** in 31% yield.

To overcome the low yield of thioether **4**, we used phenyl sulfonyl chloride as external source, as expected with 2 equivalents of it, the yield is increases to 52%.

In conclusion, this protocol offers a new, versatile, and novel approach for (a) phthalide (**2** or **3**) formation by ester cleavage of ortho substituted bromomethyl benzoate esters. (b) Desulfonation of phthalimide N-sulfonamide **2** and formation of its corresponding regioselective thioethers **4** in same reaction pot by utilizing the reduced *in situ* phenyl sulfenyl radicals. (c) Phenyl sulfonyl chloride were used as external source to generate *in situ* phenyl sulfenyl radicals, which was trapped by electron rich arenes. (d) No catalyst or additive or smelling thiol and exclusion of air are required, which avoided contamination by transition metal catalysts of the product, thioethers **4**. We believe that this environmentally friendly method will find wide applications.

General Information: All reagents unless otherwise noted were obtained from commercial sources and used without further purification. The reactions were carried out under an argon atmosphere, and the products were isolated by column chromatography on silica gel (200–300 mesh) by using hexane and ethyl acetate as eluents. Melting points are uncorrected. Compounds described in the literature was characterized by comparing their ^1H and ^{13}C NMR spectra and MS data to the reported data. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 and chemical shifts are reported in parts per million relatives to TMS. Low resolution (LR) and High-resolution (HR) mass spectrometry data were acquired on a Bruker Daltonics MicroTOF-Q-II Mass Spectrometer using $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ as solvent.

Scheme-1, Synthesis of thio-ethers

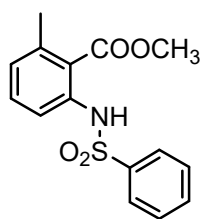


2-Methyl-6-nitrobenzoic acid methyl ester¹⁴ (6): To a pre cooled solution of 2-Methyl-6-nitrobenzoic acid (2.5 g, 13.0 mmol) in DCM (25 mL) was added oxalyl chloride (1.5 mL, 2.1 g, 16.0 mmol) and one drop of DMF under nitrogen atmosphere. Stir at 0°C-RT for 6 h. After completion, quenched the reaction with methanol at 0°C. Concentrated under reduced pressure to get the residue. Extract with EtOAc (100 mL x 2), wash the combined organic layer with water, 10% NaHCO_3 , brine, dried over MgSO_4 and filter. Concentrated under reduced pressure and flash column chromatography purification on a silica gel (elution with 1:9 EtOAc in hexane) to afforded 1.90 g (71%) of product **6**. (MP 49°C). ^1H NMR (400 MHz, CDCl_3): δ 7.78-7.77 (dd, 1H, J = 0.6 & 7.2 Hz), 7.43-7.20 (m, 2H), 4.07 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 166.8, 146.0, 137.4, 135.9, 129.7, 129.2, 121.6, 52.8, 18.7. Mass m/z : 195. HRMS m/z : 195.0532, (calculated for $\text{C}_9\text{H}_9\text{NO}_4$: 195.0532).

2-Amino-6-methylbenzoic acid methyl ester¹⁴ (7): 2-Methyl-6-nitrobenzoic acid methyl ester (**6**) (4.5 g, 23 mmol) was hydrogenated over 10% palladium charcoal (100 mg) in ethanol under atmospheric pressure of hydrogen at room temperature until the starting material disappeared (72 h). Filter and concentrated under

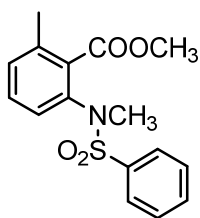
reduced pressure to get the residue. Column chromatographic purification on a silica gel (elution with 30-50% EtOAc in hexane) afforded 3.0 g of title product **7** in 80% yield. MP 15-16°C. ^1H NMR (400 MHz, CDCl_3): δ 7.10-7.01 (t, 1H, J = 7.6 Hz), 6.52-6.48 (dd, 1H, J = 0.4 & 6.8 Hz), 5.23 (br-s, 1H, NH), 3.86 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 169.6, 148.9, 140.0, 131.8, 120.3, 114.5, 113.8, 51.1, 22.6. Mass m/z : 165. HRMS m/z : 165.0788, (calculated for $\text{C}_9\text{H}_{11}\text{NO}_2$: 165.0790).

2-Benzenesulfonylamino-6-methyl-benzoic acid methyl ester¹⁵ (8): Benzene sulfonyl



chloride (3.2 g, 2.33 mL, 18 mmol, 1.0 eq) was added to a solution of 2-amino-6-methyl-benzoic acid methyl ester (**7**) (3.0 g, 18 mmol, 1.0 eq) in pyridine (15 mL) at 0°C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred 12 h. The reaction mixture was quenched by addition of water, extracted twice with EtOAc. The combined organic phases were washed with water, 10% NaHCO_3 , brine solution, dried over MgSO_4 and evaporated at reduced pressure to afford a yellow residue. Column chromatography purification (elution with 20-30% EtOAc in hexane) afforded 5.0 g of product **8** in 90% yield. MP 56°C. ^1H NMR (400 MHz, CDCl_3): δ 9.05 (br-s, 1H, NH), 7.71-7.66 (d, 2H, J = 8.4 Hz), 7.60-7.24 (m, 5H), 6.98-6.94 (d, 1H, J = 8.4 Hz). 3.70 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3): δ 168.8, 139.5, 139.1, 137.4, 132.8, 131.9, 128.9, 128.0, 127.0, 121.7, 120.6, 52.1, 22.1. Mass: m/z : 306 (M+1). HRMS m/z : 305.0725, (calculated for $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$: 305.0722).

2-(Benzenesulfonylmethylamino)-6-methyl-benzoic acid methyl ester (9): NaH (50% in oil,



475 mg, 19.6 mmol, 2.0 eq,) was washed free of oil with three 50 mL portion

of hexane and suspended in 100 mL of anhydrous DMF. To this suspension

was added methyl ester **8** (3.0 g, 9.1 mmol, 1.0 eq) and the resulting

suspension was stirred at 0°C to room temperature for 1 h. The reaction mixture was cooled to

0°C and methyl iodide (1.0 mL, 1.50 g, 11.7 mmol, 1.2 eq) was added dropwise over a period

of 10 minutes. Stir overnight (12 h) at room temperature. The reaction mixture was quenched

by cautious addition of drops of water, diluted with water, and extracted twice with EtOAc. The

combined organic phases were washed with water, brine, dried over MgSO₄ and evaporated

at reduced pressure to afford a yellow residue. Column chromatography purification (elution

with 20-30% EtOAc in hexane) afforded 2.8 g of product **9** in 89% yield. MP 134°C. ¹H NMR

(400 MHz, CDCl₃): δ 7.77-7.73 (d, 2H, *J* = 8.0 Hz), 7.62-7.42 (m, 3H), 7.27-7.17 (d, 2H, *J* =

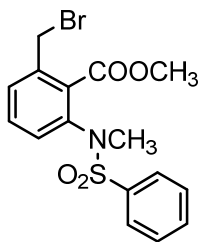
5.4 Hz), 6.64-6.60 (t, 1H, *J* = 9.0 & 4.6 Hz), 3.90 (s, 3H), 3.18 (s, 3H), 2.36 (s, 3H). ¹³C NMR

(101 MHz, CDCl₃): δ 168.1, 138.8, 138.2, 137.35 135.2, 132.8, 130.5, 129.9, 128.8, 127.9,

124.9, 52.1, 39.6, 19.6. Mass: *m/z*: 320.3 (*M*+1). HRMS *m/z* 319.0871, (calculated for

C₁₆H₁₇NO₄S: 319.0878).

2-(Benzenesulfonylmethylamino)-6-bromomethyl-benzoic acid methyl ester (1): Dissolve



2.6 g of (3.4 mmol) methyl ester **9** in CCl₄, and add NBS (1.22 g, 6.8 mmol, 2.0

eq) and catalytic amount of benzoyl peroxide (0.15 g, 0.68, 0.2 eq). Heat at

reflux for 2 hours under nitrogen atmosphere. Cool to room temperature,

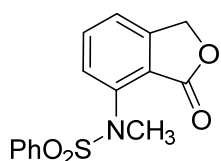
quenched with aqueous sodium metabisulfite, extract with DCM (75 mL x 2).

Wash the combined organic layer with water, 10% NaHCO₃, brine, dried over MgSO₄ and

concentrated to get the residue. Column chromatography purification (elution with 20-30%

EtOAc in hexane) afforded 1.8 g of bromo compound **1** in 61% yield. MP 112°C. ¹H NMR (400 MHz, CDCl₃): δ 7.72-7.68 (d, 2H, *J* = 7.6 Hz), 7.60-7.24 (m, 5H), 6.76-6.72 (d, 1H, *J* = 7.8 Hz), 4.63 (s, 2H), 3.93 (s, 3H), 3.21 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 166.7, 139.7, 138.0, 137.5, 134.836, 132.9, 130.7, 130.4, 128.9, 128.1, 127.8, 52.6, 39.3, 29.8. Mass: *m/z*: 398 (M⁺). HRMS *m/z* 396.9964, (calculated for C₁₆H₁₆BrNO₄S: 396.9978).

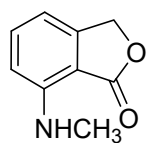
N-Methyl-N-(3-oxo-1,3-dihydro-isobenzofuran-4-yl)-benzenesulfonamide (2): To a pre-



cooled solution of trimethylsilyl iodide (240 mg, 1.2 mmol, 1.2 eq) in acetonitrile, added bromo compound **1** (397 mg, 1.0 mmol, 1.0 eq). Stir at rt for 30 minutes, then heated at reflux, monitored by tlc (3 h). After completion,

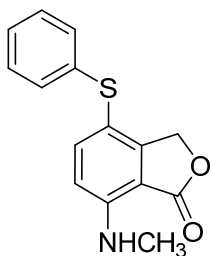
cool to room temperature and quenched by addition of water. Extract with EtOAc (25 mL x 2), Wash the combined organic layer with 10% Na₂S₂O₃ solution, brine, dried over MgSO₄ and concentrated to get the residue. Column chromatography purification (elution with 20-30% EtOAc in hexane) afforded 200 mg of title compound **2** in 65% yield. MP 144°C. ¹H NMR (200 MHz, CDCl₃): 7.75-7.41 (m, 8H), 5.21 (s, 2H), 3.32 (s, 3H). ¹³C NMR (200 MHz, CDCl₃): 167.5, 148.7, 139.8, 138.3, 134.9, 133.0, 131.1, 128.9, 127.7, 122.1, 121.8, 68.6, 38.6. Mass *m/z*: 304 (1M+1). HRMS *m/z* 303.1370, (calculated for C₁₅H₁₃NO₄S: 303.0565). Crystal data at 25°C: C₁₅H₁₃NO₄S, *M* 303.0565, Orthorhombic, *Pna*2₁, *a* = 13.5162 (13) Å, *b* = 6.9165 (6) Å, *c* = 15.090 (2) Å, *V* = 1410.7 (2) Å³, *Z* = 4, *ρ* = 0.71073 Å⁻³, *D*_x = 1.428 Mg/m⁻³, *μ* = 0.24 mm⁻¹, 1382 reflections, 191 parameters, *R* = 0.057, *R*_w 0.083 for all data.

Methylamino-3H-isobenzofuran-1-one (3): To a pre-cooled solution of trimethylsilyl iodide



(480 mg, 2.4 mmol, 2.4 eq) in acetonitrile, added bromo compound **1** (397 mg, 1.0 mmol, 1.0 eq). Stir at rt for 30 minutes, then heated at reflux, monitored by tlc (3 h). After completion, cool to room temperature and quenched by addition of water. Extract with EtOAc (25 mL x 2), Wash the combined organic layer with 10% Na₂S₂O₃ solution, brine, dried over MgSO₄ and concentrated to get the residue. Column chromatography purification (elution with 10-15% EtOAc in hexane) afforded 98 mg of title compound **3** in 60% yield. MP 86°C. ¹H NMR (400 MHz, CDCl₃): δ 7.47-7.43 (t, 1H, *J* = 7.4 Hz), 6.60-6.56 (dd, 1H, *J* = 0.6 & 6.6 Hz), 6.55-6.50 (d, 1H, *J* = 8.4 Hz), 5.18, (s, 2H), 2.92 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 173.0, 149.0, 148.0, 136.2, 108.1, 107.7, 107.5, 69.5, 29.0. Mass *m/z*: 163 (M⁺). HRMS *m/z*: 163.0632, (calculated for C₉H₉NO₂: 163.0628).

7-Methylamino-4-phenylsulfanyl-3H-isobenzofuran-1-one (4): Method-A from bromo



compound: To a pre-cooled solution of trimethylsilyl iodide (1.61 g, 8.0 mmol, 8 eq) in acetonitrile, added bromo compound **1** (397 mg, 1.0 mmol, 1.0 eq). Stir at rt for 30 minutes, then heated at reflux, monitored by tlc (5 h). After completion, cool to room temperature and quenched by addition of water. Extract with EtOAc (25 mL x 2), Wash the combined organic layer with 10% Na₂S₂O₃ solution, brine, dried over MgSO₄ and concentrated to get the residue. Column chromatography purification afforded 82 mg of title compound **4** in 30% yield. MP 108°C. ¹H NMR (200 MHz, CDCl₃): δ 7.60-7.56 (d, 1H, *J* = 8.6 Hz), 7.25-7.03 (m, 5H), 6.61-6.57 (d, 1H, *J* = 8.6 Hz), 6.47 (br-s, 1H, NH), 5.05, (s, 2H), 2.99-2.96 (d, *J* = 5.0 Hz, 3H). Mass *m/z*: 271.1 HRMS *m/z*: 271.0667, (calculated for C₁₅H₁₃NO₂S: 271.0667). Crystal data at 25°C: C₁₅H₁₃NO₂S, *M* 271.0667, orthorhombic, *Pbca*, *a* = 10.0576 (3) Å, *b* = 8.5430 (2) Å, *c* = 31.1453 (9) Å, *V* =

2676.07 (13) Å³, $Z = 8$, $a = 0.71073$ Å, $D_x = 1.347$ Mg/m³, $\mu = 0.24$ mm⁻¹, 1522 reflections, 173 parameters, $R = 0.126$, $R_w 0.127$ for all data.

Method-B from Phthalimide-7-N-sulfonamide: To a pre-cooled solution of trimethylsilyl iodide (1.2 g, 6.0 mmol, 6 eq) in acetonitrile, added Phthalimide-7-N-sulfonamide **2** (304 mg, 1.0 mmol, 1.0 eq). After Completion (3 h), workup and purification obtained 84 mg of title compound **4** in 31% yield.

Method-C from Phthalide-7-methylamine and Benenesulfonyl chloride: To a pre-cooled solution of trimethylsilyl iodide (1.2 g, 6.0 mmol, 12 eq) in acetonitrile, added Pthalimide-7-methylamine (81 mg, 0.5 mmol, 1.0 eq) and Benenesulfonyl chloride (180 mg, 1.0 mmol, 2.0 eq). After completion (4 h), workup and purification obtained 70 mg of title compound **4** in 52% yield.

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■ **Competing interests:** There is no Competing Interests pending

Data and materials availability: Crystallographic model data is available through the CCDC under identifier VABSAW, 1990780 (N-methyl-N-(3-oxo-1,3-dihydroisobenzofuran-4-yl)benzenesulfonamide **2**). VABSEA, 1990779 7-(methylamino)-4-(phenylthio)isobenzofuran-1(3H)-one, **4**).

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