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Microwave-Assisted Efficient Methylation of Alkyl and Arenesulfonamides with Trimethylsulfoxonium Iodide and KOH

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Abstract: A solvent-free synthesis of *N*-methyl and *N*,*N*-dimethylsulfonamides has been achieved by treating the primary and secondary sulfonamides with $Me_3S^+OI^-$ and KOH under microwave irradiation on alumina support.

Keywords: Microwave, solvent-free synthesis, sulfonamide, trimethylsulfoxonium iodide

INTRODUCTION

N,N-Dimethylsulfonamides are useful as photopolymerizable catalysts, fillers in dental materials, herbicides, and mildew- and rot-resisting materials for paper. Besides this, they are important constituents of volatile components of oakmass oleoresin and fresh yellow mobin fruits. They also form part of the catalyst used in Suzuki and amination cross-coupling reactions.[1] Most commonly, aromatic dimethylsulfonamides are synthesized through the condensation of arenesulfonyl chloride with dimethyl amine.[2] Several other approaches have also been used for preparation of *N*-mono- and *N,N*-dimethylsulfonamides, such as pseudomolecular rearrangement,[3] phase transfer catalyzed (PTC) *N*-alkylation,[4] electrophilic substitution of arene with $ClSO_2NR_2$,[5] and intramolecular[6] and intermolecular[1,7–9] displacement reactions. Although these approaches gave *N*-mono- and *N,N*-dimethylsulfonamides, they generally suffer from drawbacks such as long reaction times, formation of

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by-products, unsatisfactory yields, cumbersome experimental procedures, and use of hazardous solvents and expensive catalysts.

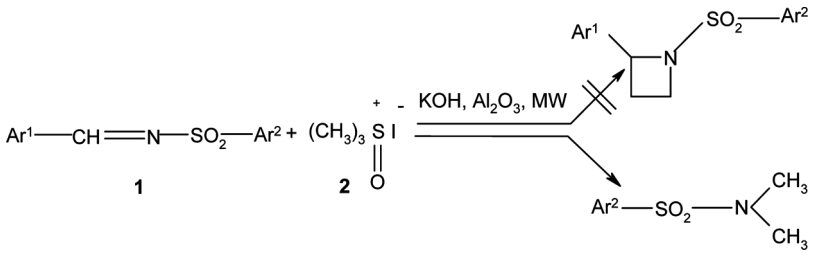
We have shown previously[10] that methylene transfer from dimethylsulfoxonium methylide to *N*-arenesulfonylimines leads to a one-pot synthesis of 2-aryl-*N*-arenesulfonylazetidines. In these reactions, however, yields were modest because of solvent-phase conformational mobility.

The demand for increasingly clean and efficient chemical synthesis is important from both economic and environmental points of view. One commonly used method is a combination of microwave irradiation and solid support. This offers a number of advantages such as environmentally friendliness, shorter reaction times, efficiency, high yields and easy workups.[11,12]

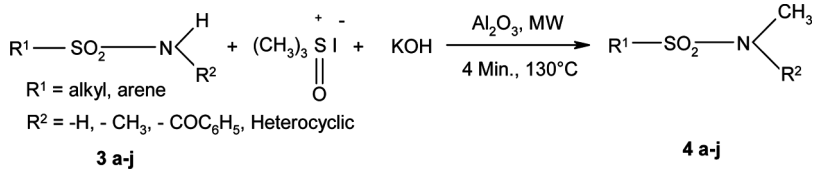
RESULTS

During the course of our investigations pertaining to microwave-assisted reactions on solid supports,[13] we tried synthesis of 2-aryl-*N*-arenesulfonylazetidines by using N-arenesulfonylimines **1**, trimethylsulfoxonim iodide **2**, and potassium hydroxide (KOH) under microwave irradiation. To our surprise, however, the only product obtained on workup was the corresponding *N,N*-dimethylarenesulfonamide (Scheme 1).

We surmised that the product arises from hydrolysis of the imines to the corresponding sulfonamide, which then gets methylated. Although Nddaka et al.[14] previously reported the synthesis of *N,N*-dimethylated sulfonamides from *N*-sulfonyltellurimides, the formation of these compounds from its carbon analog is not known. To test these ideas, several arenesulfonamides **3a–j** were treated with trimethylsulfoxonium iodide **2** and KOH under microwave irradiation on solid support to get the corresponding *N,N*-dimethylated products. Thus, herein we report a facile,



Scheme 1. Formation of *N,N*-dimethylarenesulfonamides from *N*-arenesulfonylimines under microwave irradiation.



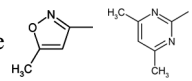
Scheme 2. Synthesis of *N*-mono- and *N,N*-dimethyl alkyl and arenesulfonamides by trimethylsulfoxonium iodide and KOH under microwave irradiation.

noncatalytic, solvent-free method for the synthesis of *N*-mono- and *N,N*-dimethyl alkyl and arenesulfonamides **4a–j** under microwave irradiation using trimethylsulfoxonium iodide and KOH as methylating agent (Scheme 2).

Some of the results we obtained for the preparation of *N*-mono and *N,N*-dimethylated alkyl and arenesulfonamides are summarized in Table 1. All products (reported in Table 1) are known in literature, except **4e**, **4i**, and **4j**. It is remarkable that the reaction time is very short, and yields of the products are excellent. The primary sulfonamides can be monomethylated or dimethylated by an appropriate amount of $Me_3S^+OI^-$ and KOH (Entries **a–g**). Entries **4c–g** show that the reaction times and yields of the products are not affected significantly by the nature of the substituent (electron donating or electron withdrawing). Entries **4h–j** show that

Table 1. Various *N*-mono- and *N,N*-dimethylsulfonamides synthesized by trimethylsulfoxonium iodide and KOH[a]

Sr. no[b]	R^1	R^2	Time (min)	Temp. (°C)	Power (W)	Ref.	Yield[c] (%)
4a	$-CH_3$	$-CH_3$	4	130	640	8a	85
4b.	$-C_6H_5$	$-CH_3$	4	130	640	8a	90
4c	$4-ClC_6H_4$	$-CH_3$	4	130	640	2b	88
4d	$4-CH_3C_6H_4$	$-CH_3$	4	130	640	3	88
4e	$4-NO_2C_6H_4$	$-CH_3$	4	130	640	—	86
4f	$4-NH_2C_6H_4$	$-CH_3$	4	130	640	2b	87
4g	$4-OCH_3C_6H_4$	$-CH_3$	4	130	640	2b	90
4h	$-CH_3$	$-COC_6H_5$	4	130	640	7a	81
4i	$4-NH_2C_6H_4$	$-C_4H_4NO$[d]	4	130	640	—	91
4j	$4-NH_2C_6H_4$	$-C_6H_7N_2$[d]	4	130	640	—	92

[a]Sulfonamide: 1 mmol; trimethylsulfoxonium iodide: 2 mmol; KOH: 2 mmol.
[b]Products were characterized by IR, NMR, elemental analysis, and HRMS.
[c]Isolated, unoptimized yields.
[d]$-C_4H_4NO$ and $-C_6H_7N_2$ are 

reaction works equally well with secondary sulfonamides. The reaction proceeds cleanly, and workup is simple, involving only filtration of solid support and removal of solvent to obtain the product in high purity. Attempts to carry out these reactions with aniline, acrylamide, benzamide, and benzoic acid afforded no mono- or dimethylated products, hereby showing that the method is applicable to sulfonamides only. It should be noted that efficacy of this dry synthetic method was evaluated by comparison with the same reaction in prolonged refluxing conditions where the reactants were completely recovered. It may also be noted that the reaction was successful only when alumina was used as the solid support; it failed when silica gel or montmorillonite K-10 or KSF were used as the solid support.

CONCLUSION

In conclusion, we have described an experimentally simple and convenient process for the synthesis of *N*-methyl and *N,N*-dimethyl alkyl and arenesulfonamides by trimethylsulfoxonium iodide and KOH under microwave irradiation.

This protocol is fairly general and applicable to a wide variety of sulfonamides. The yields are excellent. Reaction times are short, and the workup procedure is simple. The advantages of this method over reported ones include simplicity, generality, rapidity, and avoidance of toxic or expensive catalysts and solvents. Moreover, to the best of our knowledge, there is no reference on the synthesis of *N*-mono- and *N,N*-dimethylsulfonamides, which works equally well for primary and secondary sulfonamides.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a DPX-300 Bruker spectrometer. Data are reported are as follows: Integration, chemical shift in parts per million (ppm) from tetramethylsilane (TMS) on the δ scale, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet doublet, and m = multiplet), and coupling constant in Hertz (Hz). Mass spectra were recorded on QSTAR Excel Applied Biosystem spectrometer. Melting points were determined using an Electron Bombay micro-melting-point apparatus and are uncorrected. For all microwave-induced reactions, a focused Pelco laboratory microwave oven was used. IR absorption spectra were recorded on a Nicolet 5DX FTIR instrument, and values are reported in centimeters^{-1}. Monitoring of reactions was carried out using silica-gel thin-layer chromatograpic (TLC) plates (Silica Merck 60

F_{254}). Spots were visualized by UV light at 254 nm. Where required, column chromatography was performed using silica gel (60–120 mesh).

General Procedure for Preparation of *N*-Mono- and *N,N*-Dimethylsulfonamides

A mixture of appropriate sulfonamide (1 mmol), trimethylsulfoxonium iodide (2 mmol), and KOH (2 mmol) was loaded on alumina (0.5 mmol). This mixture was irradiated with microwaves for the specified time (Table 1) to get *N,N*-dimethylsulfonamides. For the synthesis of *N*-monomethylsulfonamides the reactant ratio used was 1:1:1. Only a single product (as shown by TLC) was formed. The reaction was quenched by the addition of cold H_2O. The product was extracted with ethyl acetate, and removal of the solvent gave the product in high purity.

Data

***N,N*-Dimethylmethanesulfonamide 4a:** White crystalline solid; mp 46–48 °C; yield = 85%; IR: ν_{max} (cm^{-1}): 1334, 1154; ^1H (300 MHz, $CDCl_3$): $\delta = 2.78$ (s, 3H), 2.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.76$, 34.34.

***N,N*-Dimethylbenzenesulfonamide 4b:** Brown crystalline solid; mp 50–51 °C; yield = 90%; IR: ν_{max} (cm^{-1}): 1346, 1163; ^1H (300 MHz, $CDCl_3$): $\delta = 2.71$ (s, 6H), 7.53 (m, 3H), 7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 135.35$, 132.66, 128.95, 127.64, 37.87.

***N,N*-Dimethyl-4-chlorobenzenesulfonamide 4c:** Yellow crystalline solid; mp 76–77 °C; yield = 88%; IR: ν_{max} (cm^{-1}): 1315, 1136; ^1H (300 MHz, $CDCl_3$): $\delta = 2.71$ (s, 6H), 7.54 (m, 2H), 7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 139.20$, 134.02, 129.30, 129.05, 37.81.

***N,N*-Dimethyl-4-methylbenzenesulfonamide 4d:** White crystalline solid; mp 79–81 °C; yield = 88%; IR: ν_{max} (cm^{-1}): 1333, 1160; ^1H (300 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H), 2.68 (s, 6H), 7.32 (m, 2H), 7.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.47$, 135.68, 129.69, 127.22, 37.26, 22.48.

***N,N*-Dimethyl-4-nitrobenzenesulfonamide 4e:** Yellow crystalline solid; mp 154–155 °C; yield = 86%; IR: ν_{max} (cm^{-1}): 1346, 1163; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.78$ (s, 6H), 7.97 (m, 2H), 8.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.11$, 141.73, 128.78, 113.33, 37.76; CHN found (calcd.): 41.17 (41.73), 4.56 (4.34), 12.77 (12.17). $C_8H_{10}N_2O_4SNa$: 253.0259 $[M + Na]^+$: found: 253.0258.

***N,N*-Dimethyl-4-aminobenzenesulfonamide 4f:** White crystalline solid; mp 170–172 °C; yield = 87%; IR: ν_{max} (cm^{-1}): 1333, 1160; ^1H (300 MHz,

$CDCl_3$): $\delta = 2.61$ (s, 6H), 4.91 (bs, 2H) 7.23 (m, 2H), 7.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.84, 127.46, 127.11, 118.88, 37.94$.

***N,N*-Dimethyl-4-methoxybenzenesulfonamide 4g:** Brown crystalline solid; mp 71–72 °C; yield = 90%; IR: ν_{max} (cm^{-1}): 1335, 1154; ^1H (300 MHz, $CDCl_3$): $\delta = 2.74$ (s, 6H), 3.82 (s, 3H), 7.01 (m, 2H), 7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.90, 132.90, 129.83, 114.13, 55.57, 37.95$.

***N*-Benzoyl-*N*-methyl-4-methylbenzenesulfonamide 4h:** White crystalline solid; mp 65–66 °C; yield = 81%; IR: ν_{max} (cm^{-1}): 1693, 1331, 1159; ^1H (300 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 2.63 (s, 3H), 7.34 (m, 3H), 7.52 (m, 4H), 7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 200.01, 150.01, 128.88, 127.49, 127.11, 123.44, 114.67, 38.12, 23.22.

4-Amino-*N*-(5-methyl-3-isoxazolyl)-*N*-methylbenzenesulfonamide 4i: Yellow brown crystalline solid; mp 82–84 °C; yield = 91%; IR ν_{max}(cm^{-1}): 3477, 3334, 3201, 1343, 1158; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H), 3.16 (s, 3H), 4.42 (bs, 2H), 6.42 (s, 1H), 6.51 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.03, 161.03, 151.36, 129.30, 124.52, 113.94, 97.55, 34.86, 12.59$; CHN found (calcd.): 49.91 (49.43), 4.56 (4.86), 15.55 (15.73). $C_{11}H_{14}N_3O_3S$: 268.0756 $[M + H]^+$: found: 268.0755.

4-Amino-*N*-(4,6-dimethyl-2-pyrimidinyl)-*N*-methylbenzenesulfonamide 4j: Yellow brown crystalline solid; mp 215–217°C; yield = 92%; IR ν_{max}(cm^{-1}): 3471, 3375, 3249, 1365, 1149, ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 6H), 3.62 (s, 3H), 4.09 (bs, 2H), 6.61 (d, $J = 6.9$ Hz, 2H), 7.26 (s, 1H), 7.82 (d, $J = 7.2$ Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 167.06, 150.46, 131.14, 114.08, 113.03, 33.73, 23.66; CHN found (calcd.): 54.12 (53.97), 4.56 (4.49), 19.01 (19.37). $C_{13}H_{16}N_4O_2SNa$: 315.0892 $[M + Na]^+$: found: 315.0890.

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