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A Simple and Efficient Direct Method for the Synthesis of Symmetric Dibenzyl Sulfones from Sodium Dithionite and Benzyl Chlorides in Ionic Liquid

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Summary. Symmetric dibenzyl sulfones were synthesized in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([*bmim*]BF_4) at 100°C from various benzyl chlorides and sodium dithionite in moderate yields.

Keywords. Dibenzyl sulfones; Sodium dithionite; Benzyl chloride; Ionic liquid; Synthesis.

Introduction

The use of sulfones in organic synthesis has become increasing important in recent years [1]. From the methodological point of view, sulfones have been employed in the preparation and functionalization of a wide variety of products by stabilizing α-radicals [2], α-anions [3], and acting as cationic synthons [4]. Sulfones are also widely used in medicinal chemistry and found on numerous drugs, including the recently developed selective COX-2 inhibitor Vioxx [5].

The most common and straightforward procedure for the preparation of sulfones is the oxidation of the corresponding sulfides and sulfoxides [6]. Other methods may include the alkylation of sulfinate salts [7], *Friedel-Crafts* type reaction of sulfonyl chlorides [8], and coupling reaction of aryl halides and sulfinic acid salts [9]. But these protocols often suffer from drawbacks such as side reactions, limited substrate sources, toxic solvents, irritant and foul smell, low yields, and so on, and thus reduce their scope of application. More recently, the metal mediated cross coupling reactions of sulfinate salts with halides and triflates were reported as mild alternatives to these previous methods. Among these synthetic strategies, only a few direct synthetic methods were observed for preparation of symmetric dibenzyl sulfones.

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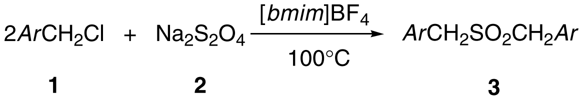
In 1964, *Wellisch et al.* [10] reported a one step synthesis of dibenzyl sulfones by the reaction of sodium dithionite with benzyl chloride in *DMF* at 110°C for 9 h with a yield of 17%. Then, *Amiri et al.* [11] in 1978 also prepared the di-α-methylenenaphthyl sulfone with the similar method in *DMSO* at 110°C for 9 h with a yield of 18%. However, these procedures have suffered from disadvantages such as limited number of substrates, low yield, and long reaction time. Therefore, further improvements to synthesize these sulfones would be desirable.

The development of environmentally friendly solvents for organic chemistry is an area of considerable importance. From both economical and environmental points of view, the use of ionic liquids as solvents has attracted much interesting recently, partly due to their polar nature, their phase behavior, and their lack of vapour pressure.

Based on our previous works at ionic liquids and inspired by relative studies reported in literature, we have explored the direct synthesis of symmetric dibenzyl sulfones from sodium dithionite and benzyl chlorides in ionic liquid 1-butyl-3-methylimmidazolium tetrafluoroborate ([*bmim*]BF_4).

Results and Discussion

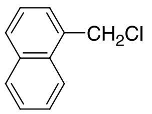
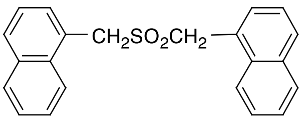
The general process is shown in Scheme 1 in which sodium dithionite reacts with a series of benzyl chlorides to produce corresponding symmetric dibenzyl sulfones.



$$\underset{\mathbf{1}}{2Ar\mathrm{CH_2Cl}} + \underset{\mathbf{2}}{\mathrm{Na_2S_2O_4}} \xrightarrow[100^\circ\mathrm{C}]{[bmim]\mathrm{BF_4}} \underset{\mathbf{3}}{Ar\mathrm{CH_2SO_2CH_2}Ar}$$

Scheme 1

Table 1. Synthesis of symmetric dibenzyl sulfones from sodium dithionite and benzyl chlorides

Entry	Benzyl chloride	Product[a]	Time/h	Yield[b]/%
a	$C_6H_5CH_2Cl$	$(C_6H_5CH_2)_2SO_2$	4	78 (76)[c]
b	$2\text{-}FC_6H_4CH_2Cl$	$(2\text{-}FC_6H_4CH_2)_2SO_2$	6	70
c	$3\text{-}FC_6H_4CH_2Cl$	$(3\text{-}FC_6H_4CH_2)_2SO_2$	6	53
d	$4\text{-}FC_6H_4CH_2Cl$	$(4\text{-}FC_6H_4CH_2)_2SO_2$	6	78
e	$2\text{-}ClC_6H_4CH_2Cl$	$(2\text{-}ClC_6H_4CH_2)_2SO_2$	6	57
f	$3\text{-}ClC_6H_4CH_2Cl$	$(3\text{-}ClC_6H_4CH_2)_2SO_2$	6	50
g	$4\text{-}ClC_6H_4CH_2Cl$	$(4\text{-}ClC_6H_4CH_2)_2SO_2$	6	57
h	$2\text{-}MeC_6H_4CH_2Cl$	$(2\text{-}MeC_6H_4CH_2)_2SO_2$	6	66
i	$3\text{-}MeC_6H_4CH_2Cl$	$(3\text{-}MeC_6H_4CH_2)_2SO_2$	6	73
j	$4\text{-}MeC_6H_4CH_2Cl$	$(4\text{-}MeC_6H_4CH_2)_2SO_2$	6	77
k			5	75

[a] Products were characterized by their IR spectra, ^1H NMR, mass spectra, and elemental analysis; [b] isolated yields based on benzyl chloride; [c] yield in parenthesis is based on the recovered ionic liquid

Sodium dithionite when treated with various benzyl chlorides in ionic liquid [*bmim*]BF_4 affords sulfones in moderate to good yields. In most cases, the reaction was completed in about 4–6 h at 100°C. The results are shown in Table 1.

Compared with the two previous results in *DMF* [10] and *DMSO* [11], our ionic liquid system was superior to them in many aspects such as rate and yield.

To explore the scope of this reaction, we extended the reaction of sodium dithionite with various benzyl chlorides carrying either electron withdrawing or electron releasing constituents in aromatic cycles. Benzyl chlorides bearing either an electron withdrawing or an electron donating group in the *ortho*-position of the aromatic ring give lower yields owing to their higher steric hindrance (Table 1, entries b, e, and h). When the electron withdrawing group was at the *meta*-position on the aromatic ring of the benzyl chloride, the yield of sulfone was slightly poorer than when the same group was at another position (Table 1, entries c and f). When there was a chloride on the aromatic cycle of the benzyl chloride, they worked less efficient to form sulfones than with other substituents.

Another merit of the ionic liquid is that it is recyclable as reaction medium. In view of environmentally friendly methodologies, recovery and reuse of the ionic liquid is highly preferable. [*bmim*]BF_4 is easily separated from the water media after the quench of the reaction and it can be recovered and reused for a next run without loss of efficiency after removal of the organic extractant.

In conclusion, we have devised a simple and efficient direct one pot synthesis of symmetric dibenzyl sulfones. This protocol is featured by easy availability of starting materials, mild conditions, simple manipulation, ease of isolation of the products, and it is benign to the environment.

Experimental

Melting points were measured on an Electrothemal X6 microscopy digital melting point apparatus and are uncorrected. IR spectra were recorded on a Bruke Equinox-55 spectrometer using KBr pellets. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE 300 (300 MHz) instrument with *TMS* at $\delta = 0.00$ ppm or the residual $CHCl_3$ at $\delta = 7.24$ ppm as an internal standard. Mass spectra were performed on a QP5050A GC-MS. Elemental analyses were obtained from a Vario EL elemental analyzer; results agreed favorably with calculated values. Chemicals used were of commercial grade without further purification.

General Procedure for the Synthesis of Symmetric Dibenzyl Sulfones ***3a–3k***

A mixture of benzyl chloride (5 mmol), sodium dithionite (3 mmol), and ionic liquid [*bmim*]BF_4 (3 cm^3) was stirred at 100°C for about 4–6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into distilled water (10 cm^3). The precipitated solid was filtered off and washed with water. The crude products were purified by recrystallization with ethanol water mixtures. The ionic liquid was recovered by extracting the water phase with dichloromethane and was used in subsequent runs after removing the dichloromethane.

Dibenzyl sulfone (**3a**, $C_{14}H_{14}SO_2$)

Yield 78%; mp 150–152°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.41 (m, 10H), 4.11 (s, 4H) ppm; IR (KBr): $\bar{\nu} = 3103$, 3062, 3034, 2985, 2937, 2856, 1637, 1605, 1545, 1495, 1453, 1409, 1297, 1120, 817, 765, 722, 619, 539 cm^{-1}; MS (70 eV): $m/z = 246$ (M^+, 1), 182 (10), 91 (100).

Di(2-flourobenzyl) sulfone (**3b**, $C_{14}H_{12}F_2SO_2$)
Yield 75%; mp 160–162°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.53 (m, 2H, Ar–H), 7.40–7.42 (m, 2H, Ar–H), 7.13–7.24 (m, 4H, Ar–H), 4.33 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3083$, 3007, 2952, 1620, 1586, 1495, 1456, 1418, 1309, 1236, 1193, 1134, 1091, 905, 853, 769, 703, 657, 618 cm^{-1}; MS (70 eV): $m/z = 282$ (M^+, 1), 218 (36), 109 (100).

Di(3-flourobenzyl) sulfone (**3c**, $C_{14}H_{12}F_2SO_2$)
Yield 53%; mp 152–154°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$–7.44 (m, 2H, Ar–H), 7.11–7.17 (m, 6H, Ar–H), 4.16 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3065$, 2983, 2933, 1589, 1486, 1448, 1416, 1308, 1271, 1237, 1150, 1123, 1078, 948, 898, 797, 760, 689, 636 cm^{-1}; MS (70 eV): $m/z = 282$ (M^+, 3), 218 (27), 109 (100).

Di(4-flourobenzyl) sulfone (**3d**, $C_{14}H_{12}F_2SO_2$)
Yield 78%; mp 190–191°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.40 (m, 4H, Ar–H), 7.09–7.15 (m, 4H, Ar–H), 4.13 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3052$, 2980, 2935, 1607, 1511, 1418, 1311, 1287, 1240, 1161, 1130, 842, 787, 751, 563, 531 cm^{-1}; MS (70 eV): $m/z = 282$ (M^+, 1), 218 (19), 109 (100).

Di(2-chlorobenzyl) sulfone (**3e**, $C_{14}H_{12}Cl_2SO_2$)
Yield 57%; mp 189–191°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$–7.58 (m, 2H, Ar–H), 7.46–7.49 (m, 2H, Ar–H), 7.32–7.37 (m, 4H, Ar–H), 4.51 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3081$, 3002, 2959, 1638, 1575, 1475, 1440, 1413, 1317, 1285, 1125, 1046, 823, 776, 739, 677, 616, 523, 485 cm^{-1}; MS (70 eV): $m/z = 314$ (M^+, 0.5), 250 (6), 127 (31), 125 (100).

Di(3-chlorobenzyl) sulfone (**3f**, $C_{14}H_{12}Cl_2SO_2$)
Yield 50%; mp 197–198°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.42 (m, 6H, Ar–H), 7.27–7.30 (m, 2H, Ar–H), 4.13 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3076$, 2996, 2946, 1594, 1577, 1477, 1312, 1276, 1123, 1088, 909, 863, 805, 742, 685, 633, 533, 482 cm^{-1}; MS (70 eV): $m/z = 314$ (M^+, 2), 250 (11), 127 (64), 125 (100).

Di(4-chlorobenzyl) sulfone (**3g**, $C_{14}H_{12}Cl_2SO_2$)
Yield 57%; mp 249–250°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$ (d, 4H, $J = 2$ Hz, Ar–H), 7.42 (d, 4H, $J = 2$ Hz, Ar–H), 4.11 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3064$, 2991, 2942, 2853, 1642, 1597, 1490, 1453, 1411, 1306, 1274, 1118, 1018, 816, 739, 642, 583, 510 cm^{-1}; MS (70 eV): $m/z = 314$ (M^+, 1), 250 (10), 127 (64), 125 (100).

Di(2-methylbenzyl) sulfone (**3h**, $C_{16}H_{18}SO_2$)
Yield 66%; mp 169–171°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–7.39 (m, 2H, Ar–H), 7.24–7.31(m, 6H, Ar–H), 4.32 (s, 4H, $2CH_2$), 2.38 (s, 6H, $2CH_3$) ppm; IR (KBr): $\bar{\nu} = 3060$, 3023, 2953, 2919, 2865, 1494, 1457, 1417, 1314, 1287, 1120, 792, 754, 620, 597, 570, 516, 482 cm^{-1}; MS (70 eV): $m/z = 274$ (M^+, 0.5), 210 (10), 105 (100).

Di(3-methylbenzyl) sulfone (**3i**, $C_{16}H_{18}SO_2$)
Yield 73%; mp 116–118°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.35 (m, 2H, Ar–H), 7.20–7.25 (m, 6H, Ar–H), 4.13 (s, 4H, $2CH_2$), 2.40 (s, 6H, $2CH_3$) ppm; IR (KBr): $\bar{\nu} = 3060$, 3023, 2953, 2919, 2865, 1494, 1457, 1417, 1314, 1287, 1120, 792, 754, 620, 597, 570, 516, 482 cm^{-1}; MS (70 eV): $m/z = 274$ (M^+, 2), 210 (11), 105 (100).

Di(4-methylbenzyl) sulfone (**3j**, $C_{16}H_{18}SO_2$)
Yield 77%; mp 204–206°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.10$ Hz, 4H, Ar–H), 7.22 (d, $J = 8.14$ Hz, 4H, Ar–H), 4.10 (s, 4H, $2CH_2$), 2.39 (s, 6H, $2CH_3$) ppm; IR (KBr): $\bar{\nu} = 3031$, 2973,

2925, 2863, 1647, 1613, 1514, 1449, 1416, 1307, 1283, 1118, 1036, 818, 766, 697, 603, 517 cm^{-1}; MS (70 eV): $m/z = 274$ (M^+, 1), 210 (8.5), 105 (100).

Di(2-methylenenaphthyl) sulfone (**3k**, $C_{22}H_{18}SO_2$)
Yield 75%; mp 218–219°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$–8.00 (m, 6H, Ar–H), 7.44–7.61 (m, 8H, Ar–H), 4.76 (s, 4H, $2CH_2$) ppm; IR (KBr): $\bar{\nu} = 3047$, 3006, 2952, 2856, 1637, 1596, 1512, 1419, 1301, 1215, 1119, 1016, 778, 739, 553, 508, 479 cm^{-1}; MS (70 eV): $m/z = 346$ (M^+, 3), 282 (6.7), 141 (100).

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