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Sulfonylation of C(sp^3)–H bond for synthesis of 2-sulfolmethyl azaarenes catalyzed by TBAI in water

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Abstract

A tetrabutylammonium iodide (TBAI)-catalyzed method for synthesis of 2-sulfolmethyl quinolone has been developed. Using water as solvent, a wide range of 2-sulfolmethyl quinolones were obtained in high to excellent yield. In addition, water and TBAI could be reused for five times without significant decrease of the yield of the corresponding product.

Keywords Sulfonylation · TBAI · Water · Azaarenes

Introduction

Organosulfones are important intermediates in organic synthesis and have been widely used in the fields of pharmaceutical chemistry, macromolecular chemistry, and agrochemicals [1–6]; For example, compound Z1 can be used as a leukotriene antagonist and inhibitor of leukotriene biosynthesis [7], and Z2 can be used as an antibacterial agent [8] (Fig. 1). Organosulfones are also important intermediates in Ramberg–Bäcklund and Julia–Lythgoe reactions [9–11]. Because of the importance of organosulfone compounds in various fields, their synthesis has attracted considerable interest. Traditionally, sulfonyl chlorides were used as sulfonyl reagent [12, 13], but they are water sensitive and have strong smell. Due to their advantages including commercial availability, water and air insensitivity, and easy handling, sulfites have been widely used in sulfonyl reactions in recent years [14–16]. An iodine-catalyzed direct sulfonylation of pyrazolones with sodium

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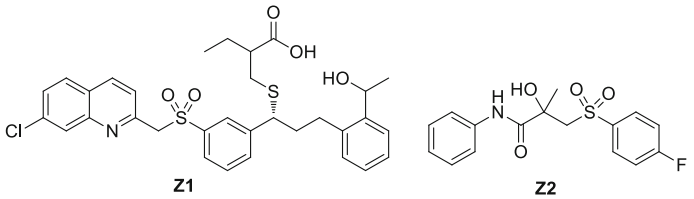


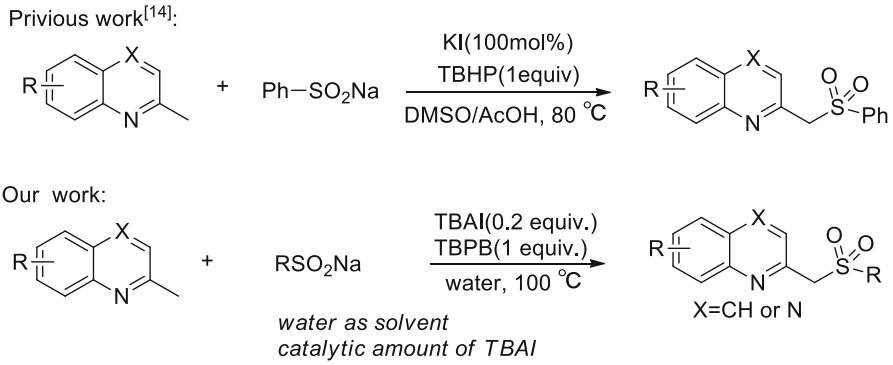
Fig. 1 Selected organosulfone compounds

sulfinates was developed by Wang and coworkers [17]. In 2017, Liu's group presented a method for synthesis of (*E*)-β-iodo vinylsulfones by reaction of alkynes with sodium sulfinates at room temperature [18].

Because of their low cost, nontoxicity, ready availability, and ecofriendly properties, iodine reagents have been widely used as metal-free catalysts to promote diverse organic transformations in recent decades [19–23]. In presence of iodine reagents, C–C bond [24–26], C–O bond [27, 28], C–N bond [29–31], and other reactions [32, 33] have been realized smoothly. In 2015 [34], Deng and coworkers presented sulfonylation of 2-methylquinolines promoted by KI (1 equiv) and *tert*-butyl hydroperoxide (TBHP). As part of our continuing effort to use iodine reagents [35–38] to mediate organic transformations, we describe herein TBAI-catalyzed sulfonylation of 2-methylquinolines with sodium sulfinates using water as solvent (Scheme 1).

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz for protons using JOEL JNM-ECA spectrometers. ^{1}H NMR chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) ($\delta = 0.0$). Chemical shifts for ^{13}C NMR spectra are reported in ppm from tetramethylsilane with the solvent as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad



Scheme 1 Sulfonylation of C(sp^3)–H bond for synthesis of 2-sulfolmethyl azaarenes

signal), integration, coupling constant (Hz), and identification. All major chemicals and solvents were obtained from commercial sources and used without further purification.

General procedure A sealable reaction tube equipped with a magnetic stirrer bar was charged with azaarenes (1.0 mmol), sodium benzenesulfinate (2 equiv), TBAI (0.2 equiv), *tert*-butyl peroxybenzoate (TBPB, 1 equiv), and water (1 ml). The reaction was carried out at 100 °C. After completion, the result was diluted with diethyl ether, washed with water and brine, and dried with Mg_2SO_4. After solvent removal under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding product.

2-((Phenylsulfonyl)methyl)quinoline (3a) Off-white (87 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.62–7.53 (m, 3H), 7.46 (t, J = 9.8 Hz, 3H), 7.30 (t, J = 7.8 Hz, 2H), 4.67 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.25 (s), 147.80 (s), 138.30 (s), 136.97 (s), 133.82 (s), 129.93 (s), 129.04 (d, J = 17.3 Hz), 128.52 (s), 127.61 (s), 127.28 (d, J = 19.2 Hz), 122.76 (s), 65.14 (s).

2-(((4-Chlorophenyl)sulfonyl)methyl)quinoline (3b) White solid (76 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.86–7.71 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 10.1 Hz, 4H), 7.28 (d, J = 8.3 Hz, 2H), 4.65 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.03 (s), 147.83 (s), 140.59 (s), 137.09 (s), 136.71 (s), 130.09 (s), 129.19 (d, J = 15.8 Hz), 127.64 (s), 127.35 (d, J = 1.7 Hz), 122.72 (s), 65.21 (s).

2-(((4-Fluorophenyl)sulfonyl)methyl)quinoline (3c) Brown solid (69 %),^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 9.1 Hz, 2H), 7.56 (dd, J = 13.5, 7.0 Hz, 3H), 7.52–7.35 (m, 2H), 6.95 (t, J = 8.1 Hz, 2H), 4.64 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.89 (s), 164.85 (s), 149.16 (s), 147.80 (s), 137.04 (s), 134.24 (d, J = 3.1 Hz), 131.49 (d, J = 9.7 Hz), 130.04 (s), 129.10 (s), 127.64 (s), 127.32 (d, J = 3.9 Hz), 122.73 (s), 116.33 (s), 116.15 (s), 65.29 (s).

2-((Methylsulfonyl)methyl)quinoline (3d) White solid (79 %),^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 6.8 Hz, 2H), 4.54 (s, 2H), 2.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.95 (s), 147.97 (s), 137.53 (s), 130.23 (s), 129.17 (s), 127.79 (s), 127.59 (s), 127.42 (s), 122.90 (s), 63.70 (s), 40.09 (s).

2-(Tosylmethyl)quinoline (3e) White solid (75 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 9.5 Hz, 4H), 7.21 (d, J = 7.7 Hz, 2H), 4.73 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.40 (s), 147.87 (s), 144.83 (s), 136.87 (s), 135.46 (s), 129.85 (s), 129.62 (s), 129.20 (s), 128.52 (s), 127.61 (s), 127.37 (s), 127.14 (s), 122.75 (s), 65.32 (s), 21.63 (s).

7-Chloro-2-(((4-chlorophenyl)sulfonyl)methyl)quinoline (3f) Yellow solid (88 %), ^{1}H NMR (500 MHz, DMSO) δ 8.42 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H),

7.82 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.64 (t, $J = 8.0$ Hz, 3H), 7.57 (d, $J = 8.4$ Hz, 1H), 5.11 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 151.66 (s), 147.91 (s), 139.56 (s), 137.93 (s), 137.38 (s), 135.02 (s), 130.62 (s), 130.42 (s), 129.79 (s), 128.21 (s), 127.58 (s), 126.03 (s), 124.22 (s), 63.75 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NCl_2S$ $[M + H]^+$: 351.99603; found: 351.99582.

7-Chloro-2-((phenylsulfonyl)methyl)quinoline (3g) White solid (91 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.73 (s, 1H), 7.65 (d, $J = 8.7$ Hz, 1H), 7.59 (d, $J = 7.9$ Hz, 2H), 7.49 (dd, $J = 15.2$, 7.9 Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 1H), 7.34 (t, $J = 7.6$ Hz, 2H), 4.63 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.44 (s), 148.13 (s), 138.20 (s), 136.72 (s), 135.76 (s), 133.96 (s), 129.05 (s), 128.85 (s), 128.47 (s), 128.22 (d, $J = 9.8$ Hz), 125.68 (s), 122.96 (s), 65.12 (s).

7-Chloro-2-(tosylmethyl)quinoline (3h) Off-white solid (77 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, $J = 8.4$ Hz, 1H), 7.88 (s, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.59 (dd, $J = 14.7$, 8.1 Hz, 3H), 7.51 (d, $J = 8.7$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 2H), 4.72 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.63 (s), 148.17 (s), 144.99 (s), 136.66 (s), 135.73 (s), 135.39 (s), 129.68 (s), 128.83 (s), 128.47 (s), 128.23 (d, $J = 2.1$ Hz), 125.71 (s), 122.97 (s), 65.22 (s), 21.66 (s). HRMS: *m/z* calcd. for $C_{17}H_{15}O_2NClS$ $[M + H]^+$: 332.05065; found: 332.05045.

7-Chloro-2-(((4-fluorophenyl)sulfonyl)methyl)quinoline (3i) Yellow solid (76 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, $J = 8.4$ Hz, 1H), 7.84 (s, 1H), 7.76 (d, $J = 8.6$ Hz, 1H), 7.73–7.64 (m, 2H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.50 (d, $J = 8.6$ Hz, 1H), 7.11 (t, $J = 8.1$ Hz, 2H), 4.74 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.95 (s), 164.91 (s), 150.36 (s), 148.11 (s), 136.84 (s), 135.92 (s), 134.23 (d, $J = 3.1$ Hz), 131.43 (d, $J = 9.7$ Hz), 128.87 (s), 128.38 (s), 128.12 (s), 125.68 (s), 122.94 (s), 116.44 (s), 116.26 (s), 65.17 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NClFS$ $[M + H]^+$: 336.02558; found: 336.02542.

7-Chloro-2-((methylsulfonyl)methyl)quinoline (3j) White solid (77 %), ^{1}H NMR (500 MHz, DMSO) δ 8.48 (d, $J = 8.4$ Hz, 1H), 8.15–8.00 (m, 2H), 7.69 (d, $J = 8.6$ Hz, 2H), 4.89 (s, 2H), 3.13 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 152.70 (s), 148.03 (s), 137.57 (s), 135.06 (s), 130.45 (s), 128.14 (s), 127.83 (s), 126.15 (s), 124.36 (s), 62.39 (s), 41.23 (s). HRMS: *m/z* calcd. for $C_{11}H_{11}O_2NClS$ $[M + H]^+$: 256.01935; found: 256.01920.

2-(((4-chlorophenyl)sulfonyl)methyl)-3-methylquinoxaline (3k) White solid (66 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.3$ Hz, 1H), 7.65 (ddd, $J = 28.7$, 15.9, 7.5 Hz, 3H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.19 (s, 1H), 4.75 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.16 (s), 144.16 (s), 141.68 (s), 140.91 (s), 140.69 (s), 136.58 (s), 130.81 (s), 130.30 (s), 129.63 (s), 129.39 (s), 128.63 (d, $J = 18.9$ Hz), 62.13 (s), 23.20 (s). HRMS: *m/z* calcd. for $C_{16}H_{14}O_2N_2ClS$ $[M + H]^+$: 333.04590; found: 333.04578.

2-Chloro-3-((phenylsulfonyl)methyl)quinoxaline (3l) White solid (65 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.80–7.65 (m, 4H), 7.60 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.93 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.59 (s), 143.50 (s), 141.52 (s), 140.74 (s), 138.68 (s), 134.25 (s), 131.95 (s), 130.81 (s), 129.21 (d, J = 14.6 Hz), 128.69 (s), 128.28 (s), 61.42 (s). HRMS: m/z calcd. for $C_{15}H_{12}O_2N_2ClS$ $[M + H]^+$: 319.63025; found: 319.03014.

2-((Phenylsulfonyl)methyl)quinoxaline (3m) Red solid (83 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.76–7.60 (m, 4H), 7.54 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 4.70 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.06 (s), 144.59 (s), 142.03 (s), 141.85 (s), 137.96 (s), 134.20 (s), 130.66 (d, J = 17.1 Hz), 129.43–129.17 (m), 128.52 (s), 62.88 (s).

2-Methyl-3-((phenylsulfonyl)methyl)quinoxaline (3n) White solid (65 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 1H), 7.71–7.63 (m, 2H), 7.63–7.50 (m, 4H), 7.39 (t, J = 7.5 Hz, 2H), 4.75 (s, 2H), 2.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.18 (s), 144.36 (s), 141.63 (s), 140.77 (s), 138.18 (s), 134.06 (s), 130.66 (s), 129.44 (s), 129.12 (s), 128.77 (d, J = 14.2 Hz), 128.48 (s), 62.19 (s), 23.15 (s).

2-(((4-Fluorophenyl)sulfonyl)methyl)quinolin-8-ol (3o) Gray solid (65 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.57 (dd, J = 6.8, 5.4 Hz, 2H), 7.49 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.13–6.92 (m, 3H), 4.64 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.99 (s), 164.95 (s), 151.85 (s), 147.02 (s), 137.63 (s), 137.35 (s), 134.11 (d, J = 3.1 Hz), 131.48 (d, J = 9.7 Hz), 128.65 (s), 127.63 (s), 123.48 (s), 117.77 (s), 116.42 (s), 116.24 (s), 110.71 (s), 64.89 (s). HRMS: m/z calcd. for $C_{16}H_{13}O_3NFS$ $[M + H]^+$: 318.05947; found: 318.05933.

6-Methyl-2-((phenylsulfonyl)methyl)quinoline (3p) Yellow solid (79 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 7.7 Hz, 2H), 7.64–7.48 (m, 4H), 7.42 (t, J = 7.5 Hz, 2H), 4.74 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.21 (s), 146.47 (s), 138.26 (s), 137.22 (s), 136.23 (s), 133.77 (s), 132.22 (s), 128.88 (d, J = 15.9 Hz), 128.55 (s), 127.41 (s), 126.40 (s), 122.73 (s), 65.20 (s), 21.63 (s).

2-((Phenylsulfonyl)methyl)benzo[*d*]thiazole (3q) Yellow solid (74 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.49–7.29 (m, 4H), 4.80 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.63 (s), 152.66 (s), 137.67 (s), 136.21 (s), 134.36 (s), 129.30 (s), 128.62 (s), 126.49 (s), 126.00 (s), 123.56 (s), 121.71 (s), 60.64 (s).

6-Bromo-2-(((4-fluorophenyl)sulfonyl)methyl)quinoline (3r) Yellow solid (90 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.70–7.56 (m, 4H), 7.08 (t, J = 8.2 Hz, 2H), 4.71 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.94 (s), 164.90 (s), 149.67 (s), 146.36 (s), 135.98 (s),

134.14 (d, $J = 3.1$ Hz), 133.55 (s), 131.46 (d, $J = 9.7$ Hz), 130.84 (s), 129.66 (s), 128.38 (s), 123.59 (s), 121.32 (s), 116.40 (s), 116.22 (s), 65.23 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NBrFS$ $[M + H]^+$: 379.97507; found: 379.97473.

6-Bromo-2-(tosylmethyl)quinoline (3s) Yellow solid (74 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.4$ Hz, 1H), 7.96 (s, 1H), 7.73 (s, 2H), 7.57 (dd, $J = 16.5$, 8.1 Hz, 3H), 7.21 (d, $J = 7.7$ Hz, 2H), 4.70 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.92 (s), 146.39 (s), 144.94 (s), 135.81 (s), 135.36 (s), 133.33 (s), 130.92 (s), 129.65 (d, $J = 4.0$ Hz), 128.44 (d, $J = 9.6$ Hz), 123.62 (s), 121.10 (s), 65.22 (s), 21.65 (s). HRMS: *m/z* calcd. for $C_{17}H_{15}O_2NBrS$ $[M + H]^+$: 376.00014; found: 375.99974.

6-Bromo-2-(((4-chlorophenyl)sulfonyl)methyl)quinoline (3t) Yellow solid (82 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, $J = 8.0$ Hz, 1H), 8.00 (s, 1H), 7.75 (dd, $J = 19.3$, 8.9 Hz, 2H), 7.61 (dd, $J = 20.3$, 8.0 Hz, 3H), 7.39 (d, $J = 8.0$ Hz, 2H), 4.76 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.54 (s), 146.28 (s), 140.73 (s), 136.60 (s), 136.14 (s), 133.66 (s), 130.72 (s), 130.04 (s), 129.68 (s), 129.32 (s), 128.43 (s), 123.66 (s), 121.42 (s), 64.97 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NBrClS$ $[M + H]^+$: 395.94552; found: 395.94516.

6-Bromo-2-((phenylsulfonyl)methyl)quinoline (3u) Yellow solid (92 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.88 (s, 1H), 7.71–7.54 (m, 4H), 7.49 (t, $J = 8.4$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 2H), 4.63 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.75 (s), 146.39 (s), 138.17 (s), 135.86 (s), 133.91 (s), 133.39 (s), 130.92 (s), 129.63 (s), 129.03 (s), 128.44 (d, $J = 13.1$ Hz), 123.60 (s), 121.18 (s), 65.17 (s).

6-Fluoro-2-((phenylsulfonyl)methyl)quinoline (3v) Off-white solid (82 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.4$ Hz, 1H), 7.82–7.71 (m, 1H), 7.59 (d, $J = 7.5$ Hz, 2H), 7.49 (t, $J = 7.1$ Hz, 2H), 7.34 (d, $J = 7.3$ Hz, 4H), 4.64 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.72 (s), 159.74 (s), 148.62 (d, $J = 2.8$ Hz), 144.97 (s), 138.24 (s), 136.25 (d, $J = 5.5$ Hz), 133.87 (s), 131.79 (d, $J = 9.2$ Hz), 129.01 (s), 128.50 (s), 128.04 (d, $J = 10.2$ Hz), 123.47 (s), 120.32 (s), 120.12 (s), 110.70 (s), 110.53 (s), 65.08 (s).

2-(((4-Chlorophenyl)sulfonyl)methyl)-6-fluoroquinoline (3w) White solid (82 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.4$ Hz, 1H), 7.83–7.70 (m, 1H), 7.62–7.46 (m, 3H), 7.38 (dd, $J = 15.6$, 8.6 Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 4.64 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.82 (s), 159.83 (s), 148.40 (d, $J = 2.8$ Hz), 144.95 (s), 140.67 (s), 136.67 (s), 136.42 (d, $J = 5.4$ Hz), 131.75 (d, $J = 9.3$ Hz), 130.05 (s), 129.30 (s), 128.08 (d, $J = 10.2$ Hz), 123.44 (s), 120.54 (s), 120.34 (s), 110.75 (s), 110.58 (s), 65.07 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NClFS$ $[M + H]^+$: 336.02558; found: 336.02563.

6-Fluoro-2-(((4-fluorophenyl)sulfonyl)methyl)quinoline (3x) White solid (86 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, $J = 8.4$ Hz, 1H), 7.96–7.76 (m, 1H), 7.75–7.64 (m, 2H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.44 (t, $J = 9.7$ Hz, 2H), 7.08 (t, $J = 7.9$ Hz, 2H), 4.72 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.92 (s), 164.88 (s), 161.77 (s),

159.78 (s), 148.55 (d, $J = 2.8$ Hz), 144.92 (s), 136.37 (d, $J = 5.4$ Hz), 134.21 (d, $J = 3.1$ Hz), 131.72 (d, $J = 9.3$ Hz), 131.46 (d, $J = 9.7$ Hz), 128.05 (d, $J = 10.2$ Hz), 123.46 (s), 120.47 (s), 120.27 (s), 116.38 (s), 116.19 (s), 110.75 (s), 110.57 (s), 65.14 (s). HRMS: *m/z* calcd. for $C_{16}H_{12}O_2NF_2S$ $[M + H]^+$: 320.05513; found: 320.05521.

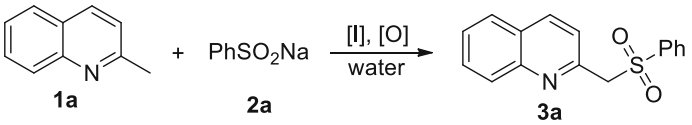
6-Fluoro-2-(tosylmethyl)quinoline (3y) White solid (83 %), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.4$ Hz, 1H), 7.98–7.79 (m, 1H), 7.65–7.51 (m, 3H), 7.44 (t, $J = 9.8$ Hz, 2H), 7.21 (d, $J = 7.7$ Hz, 2H), 4.70 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.70 (s), 159.71 (s), 148.80 (d, $J = 2.8$ Hz), 144.95 (d, $J = 12.9$ Hz), 136.18 (d, $J = 5.5$ Hz), 135.44 (s), 131.80 (d, $J = 9.2$ Hz), 129.64 (s), 128.50 (s), 128.06 (d, $J = 10.1$ Hz), 123.48 (s), 120.26 (s), 120.05 (s), 110.70 (s), 110.53 (s), 65.17 (s), 21.63 (s). HRMS: *m/z* calcd. for $C_{17}H_{15}O_2NFS$ $[M + H]^+$: 316.08020; found: 316.08008.

Results and Discussion

At the start of our studies, the reaction of 2-methylquinoline with sodium benzenesulfinate was used as model reaction under various conditions. The effects of various oxidants, iodine reagents, and temperature on the yield of the reaction were investigated; the results are summarized in Table 1. To our delight, the corresponding product was obtained in 88 % yield when *tert*-butyl peroxybenzoate (TBPB) was used as oxidant (Table 1, entry 1) in presence of tetrabutylammonium iodide (TBAI). Very low yield of product was isolated when the reaction was performed using $K_2S_2O_8$ as oxidant (Table 1, entry 4). Other oxidants (Table 1, entries 2, 3, 6) such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and oxone were ineffective with no desired product being detected. With respect to the iodine reagent species, TBAI was found to be optimal. Other iodine reagents such as NH_4I, KI, I_2O_5, and I_2 were inferior compared with TBAI (Table 1, entries 7–10). We next turned our attention to investigate the effect of the catalyst loading on the sulfonylation reaction (Table 1, entries 11–13). The yield showed no significant change when the loading of TBAI was decreased to 0.2 equiv. However, lower product yield of 61 % was obtained when only 0.1 equiv TBAI was added (Table 1, entry 13). The effect of temperature on the yield of the reaction was also examined; the results showed that 100 °C was optimal (Table 1, entries 14, 15). Therefore, the optimized reaction conditions were TBAI (0.2 equiv) and TBPB (1 equiv) in water at 100 °C for 10 h.

With the optimized reaction conditions in hand, a variety of alkyl azaarenes and sodium sulfinates were examined to illustrate the efficiency and scope of the TBAI-catalyzed sulfonylation reaction of C(sp^3)–H bond. Generally speaking, alkyl azaarenes and derivatives with electron-rich or electron-poor groups on the aryl rings could readily participate in the reaction, providing the desired product in high yield. There was no obvious electronic effect in the reaction. Alkyl azaarenes without substituent could react with various sodium sulfinates and afford the desired product in moderate to high yield (**3a–c**). Alkyl azaarenes with substituents such as

Table 1 Optimization of reaction conditions



Entry	[I] (equiv)	[O] (1 equiv)	Yield (%)[a]
1	TBAI (1)	TBPB	88
2	TBAI (1)	TBHP	NR
3	TBAI (1)	DTBP	NR
4	TBAI (1)	$K_2S_2O_8$	Trace
6	TBAI (1)	Oxone	NR
7	NH_4I (1)	TBPB	44
8	KI (1)	TBPB	Trace
9	I_2O_5 (1)	TBPB	Trace
10	I_2(1)	TBPB	Trace
11	TBAI (0.5)	TBPB	87
12	TBAI (0.2)	TBPB	87
13	TBAI (0.1)	TBPB	61
14	TBAI (0.2)	TBPB	87[b]
15	TBAI (0.2)	TBPB	75[c]

1a (0.5 mmol), **2a** (2 equiv), water (1 mL), 100 °C, 10 h

[a]Isolated yield

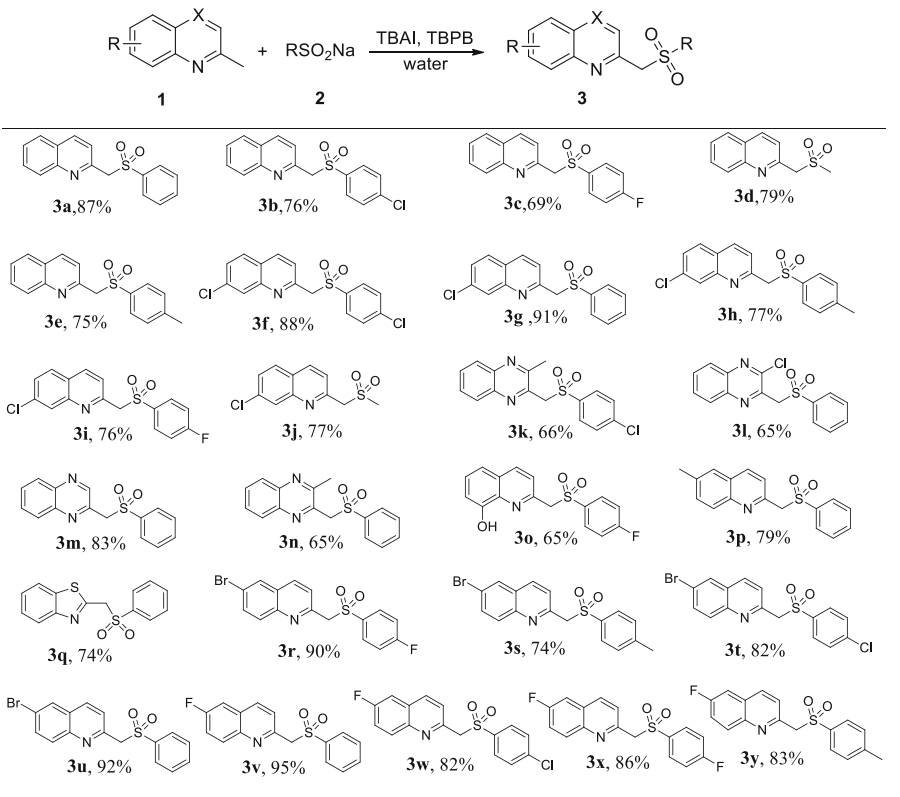
[b]Reacted at 110 °C

[c]Reacted at 90 °C

Cl, F, Br, OH, and CH_3 on the benzene ring were also well tolerated in the reaction system, reacting with sodium sulfinates to generate the corresponding product in yield of 74–95 % (**3g**, **h**, **k**–**p**, **s**–**y**). Furthermore, when 2-methylbenzo[*d*]thiazole was subjected to this reaction system, the desired product **3q** was obtained in 74 % isolated yield. Substituted sodium sulfinates with different groups were also investigated. Sodium sulfinates with electron-donating group (CH_3) or electron-withdrawing group (Cl, F) on the phenyl rings could react with alkylquinoline to give the desired product in moderate to high yield (**3e**, **f**, **r**). Note that sodium methanesulfinate also showed high reactivity for this transformation, giving the desired product **3d**, **j** in yield of 79 % and 77 %, respectively (Table 2).

Although water and TBAI are low cost, from the environmental and economic points of view, recycling of solvent and TBAI was also investigated using the reaction between 2-methylquinoline (**1a**) and sodium benzenesulfinate (**2a**). After reaction completion, the product was extracted with diethyl ether, and the water and TBAI were reused for the next time. To our delight, the recovered solvent and TBAI could be reused for five times without a significant decrease of the yield of the corresponding product **3a** (Table 3).

Table 2 Substrate scope for sulfonylation of azaarenes



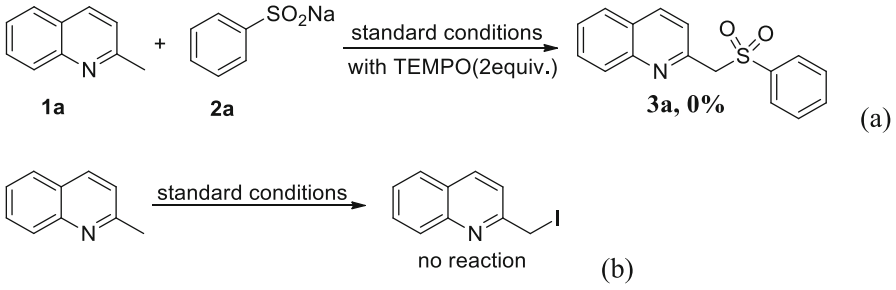
Reaction conditions: **1** (0.5 mmol), **2** (2 equiv), TBAI (0.2 equiv), TBPB (1 equiv), water (1 mL), 100 °C, 10 h. Isolated yield

Table 3 Recovery and reuse of water and TBAI

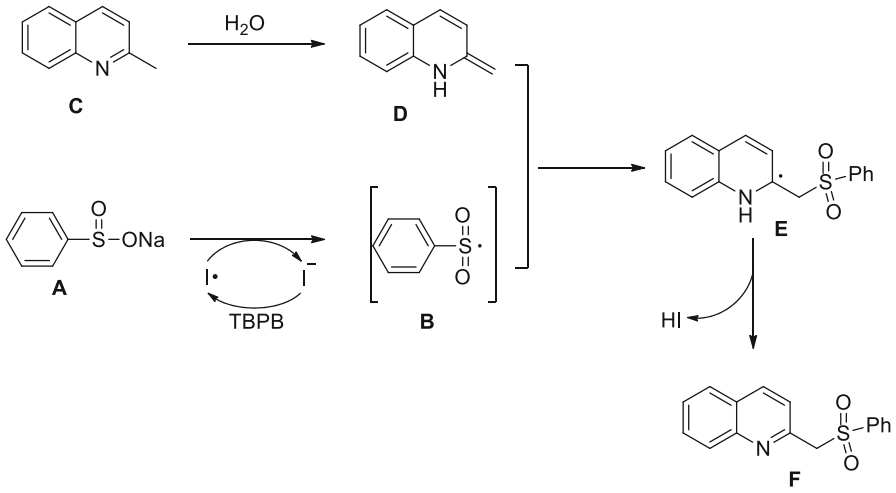
Entry	1	2	3	4	5
Yield (%)	87	87	84	82	80

1a (0.5 mmol), **2a** (2.0 equiv), TBAI (0.2 equiv), TBPB (1 equiv), water (1 mL)

To understand the reaction mechanism, a series of control experiments were conducted, as shown in Scheme 1. When 2 equiv 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added in the standard reaction conditions, the reaction was completely suppressed (Scheme 2a). If the reaction was conducted in absence of sodium benzenesulfinate, no 2-(iodomethyl)quinolone was obtained (Scheme 2b). These observations indicate that radical species may be involved in the present transformation.



Scheme 2 Control experiments



Scheme 3 A plausible reaction mechanism

Based on previous reports [34, 39–43] and our preliminary results, a possible mechanism is proposed in Scheme 3. In presence of I_2 and TBPB, sulfonyl radical **B** can be generated from sodium benzenesulfinate **A**. 2-Methylquinolone undergoes isomerization to afford intermediate **D**. Then, addition reaction between **B** and **D** affords intermediate **E**. Finally, the desired product **F** is formed with concomitant formation of HI (Scheme 3). The generated HI could be reused for the next catalytic cycle.

Conclusions

An efficient and concise method for sulfonylation of alkylazaarenes was developed. Using water as solvent and TBAI as catalyst, various desired products were obtained in high yield. Furthermore, water and TBAI could be reused for five times without a significant decrease of the yield of the corresponding product. Further investigation on the reaction mechanism and substrate scope is underway in our laboratory.

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