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Microwave Assisted Synthesis of Sodium Sulfonates Precursors of Sulfonyl Chlorides and Fluorides

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Abstract

We describe the use of a microwave reaction for the conversion of various bromides to sodium sulfonates that have been further elaborated to sulfonyl chlorides. This new approach leads to much improved yields and shorter reaction times. Representative sulfonyl chlorides serve as precursors for the respective sulfonyl fluorides that are potent inhibitors of the fatty acid amide hydrolase.

Keywords

Sodium sulfonates; Microwave; Sulfonyl chlorides; Sulfonyl fluorides

Introduction

Sulfonyl chlorides are important intermediates for the synthesis of a range of organic compounds including industrial and agricultural chemicals. For example, these are used in the preparation of sulfonic acid amides and esters as well as in the production of herbicides, detergents, dyes, elastomers, ion exchange resins and pharmaceuticals.[1–10]

In the course of our program aiming at developing potent and selective inhibitors for the endocannabinoid deactivating enzymes,[11–17] we were faced with the synthesis of substituted and unsubstituted phenylalkyl and phenoxyalkyl sulfonyl chlorides (Scheme 1) that serve as precursors for the respective sulfonyl fluorides. In general, sulfonyl fluorides (e.g. AM 374[14], **3**, Figure 1) are capable of inhibiting12–14,[18] fatty acid amide hydrolase (FAAH),[19–21] an intracellular membrane-bound enzyme that degrades and inactivates bioactive lipid amides including the endocannabinoid anandamide22 (**1a**, Figure 1) and the sleep inducing agent oleamide[23] (**2a**, Figure 1). Some sulfonyl fluorides act as FAAH inhibitors and exhibit therapeutic potential for the treatment of pain, inflammation, cancer, anxiety, and sleep disorders.[24–26]

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A general approach for the preparation of sulfonyl chlorides involves oxidative chlorination of the precursor sulfur derivatives[9, 27–38] (e.g. thiols, sulfides, thiocyanates, thiocarbamates, thioacetates, isothioureas etc.). However, many of these procedures involve stepwise oxidation followed by chlorination leading to low yields, and are not convenient and safe due to the use of hazardous and noxious reagents. Recently developed oxidizing agents such as N-chlorosuccinimide,[39,40] as well as the iodosobenzene/HCl[41] and the chloro-trimethysilane/KNO_3 [42] systems are more effective when used with aryl and benzyl thiols and thiol derivatives.

Non oxidative approaches for the synthesis of alkyl sulfonyl chlorides involve: (a) formation of Grignard or organolithium reagents from alkyl halides and subsequent addition to sulfuryl chloride;[18,43,44] and (b) refluxing of bromides with sodium or ammonium sulfite in water[45–49] to give the corresponding sulfonates that upon treatment with a chlorinating agent[45–51] (e.g. $SOCl_2$/DMF, $POCl_3$, PCl_5, cyanuric chloride etc.) lead to sulfonyl chlorides. However, use of organometalic reagents involves tedious procedures and results in poor and at best moderate yields, while conversion of bromides to sulfonates requires refluxing for many hours.

While seeking to improve the method which employs sodium sulfite in refluxing water,[45–47,49] we found that use of microwave irradiation remarkably decreases the time required for the conversion of bromides to sodium sulfonates and enhances the yield of the respective sulfonyl chlorides. Optimal conditions involve microwave heating (160°C) of bromide and sodium sulfite in a mixture of THF:EtOH:H_2O for 15 min. We report here details of this work and include the synthesis of the hitherto unknown sulfonyl fluorides **9b**, **9m** and **9n** (Scheme 2). A full structure activity relationship (SAR) study for all sulfonyl fluorides synthesized[11,12] as FAAH inhibitors will be reported elsewhere.

Results and Discussion

In order to identify optimal reaction conditions for the conversion of substituted and unsubstituted phenylalkyl and phenoxyalkyl bromides **3a–3p** to the respective sodium sulfonates **4a–4p** (Scheme 1) we have chosen **3a** and **3b** as representative starting materials for a screening process where a number of reaction conditions were explored (Table 1). The required 4-phenoxybutyl bromide (**3b**) was commercially available while 4-bromo-1-(4-benzyloxyphenyl)butane (**3a**) was synthesized in five steps from 4-phenoxybutyl bromide and 4-anisaldehyde following our disclosed procedures.[12] Bromides **3a** and **3b** were heated with sodium sulfite using reaction conditions shown in Table 1, and the crude sodium sulfonates **4a** and **4b** were treated with thionyl chloride in the presence of catalytic amounts of DMF, under standard conditions,[12,46,49] to give the respective sulfonyl chlorides **5a** and **5b**. As seen in Table 1, heating of **3a** and sodium sulfite in refluxing water for 36 hours led to sulfonyl chloride **5a** in 18% isolated yield (entry 1). The yield of this conversion was improved significantly (37%) and the heating time was reduced to 24 hours when the solvent was changed to a mixture of EtOH:H_2O (2:1 ratio, entry 2). Replacement of the conventional heating method with microwave irradiation resulted in improved yield for sulfonyl chloride **5a** (41%) while the reaction time was remarkably reduced to 10 min (entry 3). Further improvement in the yield of **5a** (47–50%) was accomplished by microwave heating at 160°C for 15 min using a mixture of THF:EtOH:H_2O (1:2:2 ratio) as the reaction solvent (entries 4–6).

Similar trends were observed in the conversion of 4-phenoxybutyl bromide (**3b**) to the respective sulfonyl chloride **5b** (Table 1). Conventional heating for 24 hours is required to produce **5b** in 58% yield, while microwave irradiation for 15 min using 1.6 equivalents of sodium sulfite, led to 62% yield for **5b** (entries 7–9). Again, use of a mixture of

THF:EtOH:H_2O (1:2:2 ratio) as the reaction solvent, enhances the yield of the two step procedure (entry 10). In summary, optimal reaction conditions for the conversion of bromides **3a** and **3b** to the respective sodium sulfonates **4a** and **4b** (Scheme 1) involve microwave irradiation (160°C) of **3a** or **3b** and 1.6 equivalents of sodium sulfite in a mixture of THF:EtOH:H_2O (1:2:2 ratio).

With these results in hand, the scope of our microwave approach was explored with a variety of substituted and unsubstituted phenylalkyl and phenoxyalkyl bromides as well as with alkyl, alkenyl and substituted alkyl bromides[52] (Scheme 1 and Table 2). The required starting materials **3c–3h**, **3m–3s**, and **6** were commercially available while bromides **3i**, **3j** and **3k** were synthesized in five steps from 6-phenoxyhexyl bromide and 4- or 3- or 2-anisaldehyde following our previously disclosed procedures.[12] Starting bromide **3l** was prepared by etherification[12] of commercially available 4-hydroxyphenol with 1,4-dibromobutane.

We have previously synthesized phenylalkyl sulfonyl chlorides **5c–5h** (Scheme 1) from the respective iodides using a low temperature lithium-iodine exchange[53] and treatment of the resulting organolithium reagent with sulfuryl chloride.[12] This approach gave **5c–5h** in only 19–23% yields[12] while following our optimized microwave assisted method the yield was increased to 60–65% (Table 2, entries 3–8). In addition, the benzyloxy substituted phenylheptyl sulfonyl chlorides **5i–5k** (Scheme 1) were previously synthesized by us in 38–40% yields using conventional heating for 24 hours,[12] whereas microwave irradiation for 15 min increased the yields to 50–52% (Table 2, entries 9–11). In a similar fashion, sulfonyl chlorides **5l–5s** and the 1,5-disulfonyl chloride **8** were synthesized in 44–65% yield (Table 2, entries 12–20). Treatment of **5b**, **5m** and **5n** with ammonium fluoride in refluxing acetone gave the respective sulfonyl fluorides **9b**, **9m** and **9n** in 90–92% yield[54] (Scheme 2).

Conclusion

In summary, we found that use of microwave irradiation remarkably decreases the time required for the conversion of bromides to sodium sulfonates and enhances the yield of the respective sulfonyl chlorides. Representatives of the latter serve as precursors for the corresponding sulfonyl fluorides that are potent inhibitors of the fatty acid amide hydrolase.

Acknowledgments

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52. Typical procedure for the conversion of bromides **3** to sulfonyl chlorides **5** via sodium sulfonates **4**.**Sulfonic acid sodium salts (4)**. A mixture of bromide **3** (1 mmol) and Na_2SO_3 (1.6 mmol) in THF/EtOH/H_2O (1:2:2 mixture, 5 mL) was heated for 15 minutes at 160°C under microwave irradiation (300 W) using a CEM Discover system. The reaction mixture was cooled to room temperature and volatiles were removed under reduced pressure. The residue was scrupulously dried under high vacuo and the crude product **4**, (a pale yellow solid) was used in the next step without further purification.**Sulfonyl chlorides (5)**. To a stirred suspension of sulfonate **4** in anhydrous benzene (7 mL)/DMF (0.1 ml), was added thionyl chloride (2.6 mmol) and the mixture was heated at 50°C for 3 hours under argon. The reaction mixture was quenched by dropwise addition of water at room temperature and extracted with diethyl ether. The organic layer was washed with brine dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (diethyl ether in hexane) gave **5** in yields shown on Table 2. Selected data of synthesized sulfonyl chlorides:**4-Phenoxybutanesulfonyl chloride (5b)**. IR (neat) 2935, 1513, 1371 (s), 1164 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.2 Hz, 2H, 3-H, 5-H, -OPh), 6.97 (t, *J* = 8.2 Hz, 1H, 4-H, -OPh), 6.89 (d, *J* = 8.2 Hz, 2H, 2-H, 6-H, -OPh), 4.04 (t, *J* = 5.7 Hz, 2H, -C*H*$_2$-OPh), 3.80 (m as t, *J* = 8.0 Hz, half of an AA'XX' system, 2H, -CH_2SO_2Cl), 2.29 (m as qt, *J* = 7.0 Hz, 2H, -C*H*$_2$$CH_2SO_2Cl$), 2.01 (qt, *J* = 6.0 Hz, 2H, -C*H*$_2$$CH_2CH_2SO_2Cl$); mass spectrum *m/z* (relative intensity) 250 (M^++2, 7), 248 (M^+, 21), 155 (16), 107 (22), 94 (100), 77 (21), 65 (15); Exact mass calculated for $C_{10}H_{13}ClO_3S$, 248.0274; found, 248.0276.**4-(2-Chlorophenoxy)butanesulfonyl chloride (5m)**. IR (neat) 2927, 1512, 1371 (s), 1163 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 3-H, -O-*Ph*-Cl), 7.24 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 5-H, -O-*Ph*-Cl), 6.94 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 4-H, -O-*Ph*-Cl), 6.93 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 6-H, -O-*Ph*-Cl), 4.13 (t, *J* = 5.8 Hz, 2H, -C*H*$_2$-O-Ph-Cl), 3.95 (m as t, *J* = 7.3 Hz, half of an AA'XX' system, 2H, -CH_2SO_2Cl), 2.35 (m as qt, *J* = 7.5 Hz, 2H, - C*H*$_2$$CH_2SO_2Cl$), 2.10 (qt, *J* = 6.0 Hz, 2H, -C*H*$_2$$CH_2CH_2SO_2Cl$); mass spectrum *m/z* (relative intensity) 286 (M^++4, 2), 284 (M^++2, 13), 282 (M^+, 19), 183 (5), 155 (31), 141 (15), 128 (100), 111 (6), 99 (7), 83 (8); Exact mass calculated for $C_{10}H_{12}Cl_2O_3S$, 281.9884; found, 281.9887.**4-(3-Methylphenoxy)butanesulfonyl chloride (5n)**. IR (neat) 2943, 1513, 1372 (s), 1164 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 1H, 5-H, -O-*Ph*-Me), 6.81 (d, *J* = 7.5 Hz, 1H, 4-H, - O-*Ph*-Me), 6.73 (s, 1H, 2-H, -O-*Ph*-Me), 6.71 (d, *J* = 7.5 Hz, 1H, 6-H, -O-*Ph*-Me), 4.04 (t, *J* = 5.5 Hz, 2H, -C*H*$_2$-O-Ph-Me), 3.81 (m as t, *J* = 7.3 Hz, half of an AA'XX' system, 2H, -CH_2SO_2Cl), 2.35 (s, 3H, -Me), 2.29 (m as qt, *J* = 7.1 Hz, 2H, -C*H*$_2$$CH_2SO_2Cl$), 2.02 (qt, *J* = 6.9 Hz, 2H, - C*H*$_2$$CH_2CH_2SO_2Cl$); mass spectrum *m/z* (relative intensity) 264 (M^++2, 3), 262 (M^+, 9), 162 (21), 147 (12), 131 (19), 119 (42), 108 (100), 91 (95), 77 (22), 64 (43); Exact mass calculated for $C_{11}H_{15}ClO_3S$, 262.0430; found, 262.0429.
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54. Typical procedure for the conversion of sulfonyl chlorides **5b**, **5m** and **5n** to fluorides **9b**, **9m** and **9n**.To a stirred solution of sulfonyl chloride **5** (1 equiv.) in dry acetone, was added anhydrous NH_4F (2.3 equiv.) and the mixture refluxed for 2 hours under argon. The solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. Purification by flash column chromatography on silica gel (diethyl ether in hexane) gave sulfonyl fluoride **9** as a white solid in 90–92% yield.**4-Phenoxybutanesulfonyl fluoride (9b)**. IR (neat) 2940, 1513, 1398 (s), 1194 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (td, *J* = 8.5 Hz, *J* = 1.0 Hz, 2H, 3-H, 5-H, -OPh), 6.97 (td, *J* = 8.5 Hz, *J* = 1.0 Hz, 1H, 4-H, -OPh), 6.89 (dd, *J* = 8.5 Hz, *J* = 1.0 Hz, 2H, 2-H, 6-H, -OPh), 4.03 (t, *J* = 5.6 Hz, 2H, -C*H*$_2$-OPh), 3.50 (m as dt, *J* = 11.0 Hz, *J* = 4.5 Hz, 2H, -CH_2SO_2F), 2.20 (m as qt, *J* = 7.5 Hz, 2H, - C*H*$_2$$CH_2SO_2F$), 2.00 (qt, *J* = 7.0 Hz, 2H, -C*H*$_2$$CH_2CH_2SO_2F$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.48, 129.58, 121.11, 114.41, 66.52, 50.65 (d, *J* = 16.4 Hz, -*C*H_2SO_2F), 27.43, 20.91; mass spectrum *m/z* (relative intensity) 232 (M^+, 25), 139 (9), 107 (6), 94 (100), 77 (13); Exact mass calculated for $C_{10}H_{13}FO_3S$, 232.0569; found, 232.0572. Anal. Calc. ($C_{10}H_{13}FO_3S$): C, 51.71; H, 5,64. Found: C, 52.09; H, 5.75.**4-(2-**

Chlorophenoxy)butanesulfonyl fluoride (9m). IR (neat) 2929, 1511, 1394 (s), 1197 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 3-H, -O-*Ph*-Cl), 7.24 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 5-H, -O-*Ph*-Cl), 6.94 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 4-H, -O-*Ph*-Cl), 6.93 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, 6-H, -O-*Ph*-Cl), 4.12 (t, *J* = 6.0 Hz, 2H, -C*H*$_2$-O-Ph-Cl), 3.64 (m as dt, *J* = 11.0 Hz, *J* = 3.5 Hz, 2H, -CH_2SO_2F), 2.26 (m as qt, *J* = 8.0 Hz, 2H, -C*H*$_2$$CH_2SO_2F$), 2.08 (q, *J* = 6.0 Hz, 2H, -C*H*$_2$$CH_2CH_2SO_2F$); mass spectrum *m/z* (relative intensity) 268 (M^++2, 7), 266 (M^+, 21), 238 (9), 196 (10), 149 (12), 139 (14), 128 (100), 99 (6); Exact mass calculated for $C_{10}H_{12}FClO_3S$, 266.0180; found, 266.0178.**4-(3-Methylphenoxy)butanesulfonyl fluoride (9n)**. IR (neat) 2954, 1515, 1398 (s), 1192 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 1H, 5-H, -O-*Ph*-Me), 6.81 (d, *J* = 7.5 Hz, 1H, 4-H, - O-*Ph*-Me), 6.73 (s, 1H, 2-H, -O-*Ph*-Me), 6.71 (d, *J* = 7.5 Hz, 1H, 6-H, -O-*Ph*-Me), 4.04 (t, *J* = 6.0 Hz, 2H, -C*H*$_2$-O-Ph-Me), 3.52 (m as dt, *J* = 11.0 Hz, *J* = 3.5 Hz, 2H, -CH_2SO_2F), 2.36 (s, 3H, -Me), 2.21 (m as qt, *J* = 7.6 Hz, 2H, -C*H*$_2$$CH_2SO_2F$), 2.00 (qt, *J* = 6.7 Hz, 2H, -C*H*$_2$$CH_2CH_2SO_2F$); mass spectrum *m/z* (relative intensity) 246 (M^+, 31), 139 (8), 128 (9), 108 (100), 91 (12), 77 (6); Exact mass calculated for $C_{11}H_{15}FO_3S$, 246.0726; found, 246.0729.

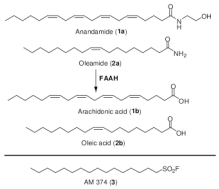
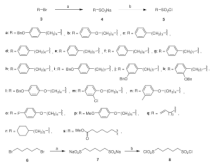
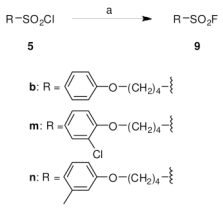


Figure 1.
Substrates (**1a**, **2a**) and inhibitor (**3**) of Fatty Acid Amide Hydrolase (FAAH).



Scheme 1.

Reagents and conditions: (a) Na_2SO_3, THF:EtOH:H_2O (1:2:2), MW, 160°C, 15 min; (b) $SOCl_2$, benzene/DMF, 50°C, 3 h, 44–65% from **3**.



Scheme 2.
Reagents and conditions: (a) NH_4F, acetone, reflux, 2 h, 90–92%.

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Table 1

Reaction conditions for the conversion of bromides **3a** and **3b** to sodium sulfonates **4a** and **4b** and yields of the final products sulfonyl chlorides[a] **5a** and **5b** respectively.

Entry	Bromide	Product Sulfonyl chloride	Solvent (equiv. of Na_2SO_3)	Heating (temp.)	Time of heating for the conversion of bromides to sodium sulfonates	Yield[b] of sulfonyl chloride
1	**3a**	**5a**	H_2O (1.4)	CH[c] (reflux)	36 h	18%
2	**3a**	**5a**	EtOH:H_2O= 2:1 (1.4)	CH[c] (reflux)	24 h	37%
3	**3a**	**5a**	EtOH:H_2O= 2:1 (1.4)	MW[d] (120°C)	10 min	41%
4	**3a**	**5a**	THF:EtOH:H_2O = 1:2:2 (1.4)	MW[d] (120°C)	10 min	47%
5	**3a**	**5a**	THF:EtOH:H_2O =1:2:2 (1.4)	MW[d] (160°C)	15 min	50%
6	**3a**	**5a**	THF:EtOH:H_2O = 1:2:2 (1.4)	MW[d] (160°C)	20 min	48%
7	**3b**	**5b**	EtOH:H_2O= 2:1 (1.4)	CH[c] (reflux)	24 h	58%
8	**3b**	**5b**	EtOH:H_2O= 2:1 (1.4)	MW[d] (150°C)	10 min	61%
9	**3b**	**5b**	EtOH:H_2O = 2:1 (1.6)	MW[d] (160°C)	15 min	62%
10	**3b**	**5b**	THF:EtOH:H_2O = 1:2:2 (1.6)	MW[d] (160°C)	15 min	65%

[a] Sulfonyl chlorides were produced from the intermediate sodium sulfonates **4a** and **4b** using standard conditions (Scheme 1).[12]

[b] Isolated yields of spectroscopically pure compounds.

[c] CH = Conventional heating inside a thermostated oil bath under magnetic stirring.

[d] MW = Microwave irradiation using a CEM Discover microwave devise in closed vessels and under magnetic stirring.

Table 2

Examples of synthesized sulfonyl chlorides using the microwave assisted approach.[a]

Entry	Bromide	Sulfonyl chloride	Yield[b]
1	**3a**	**5a**	50%
2	**3b**	**5b**	65%
3	**3c**	**5c**	61%
4	**3d**	**5d**	65%
5	**3e**	**5e**	65%
6	**3f**	**5f**	63%
7	**3g**	**5g**	60%
8	**3h**	**5h**	61%
9	**3i**	**5i**	52%
10	**3j**	**5j**	51%
11	**3k**	**5k**	50%
12	**3l**	**5l**	51%
13	**3m**	**5m**	63%
14	**3n**	**5n**	65%
15	**3o**	**5o**	52%
16	**3p**	**5p**	53%
17	**3q**	**5q**	55%
18	**3r**	**5r**	57%
19	**3s**	**5s**	51%
20	**6**	**8**	44%

[a] Reagents and conditions: (a) Na_2SO_3, THF:EtOH:H_2O (1:2:2), MW, 160°C, 15 min; (b) $SOCl_2$, benzene/DMF, 50°C, 3 h.

[b] Isolated yields of spectroscopically pure compounds.