A Sulfonative rearrangement of *N*-Aryl Sulfamates to *para*-Sulfonyl Anilines

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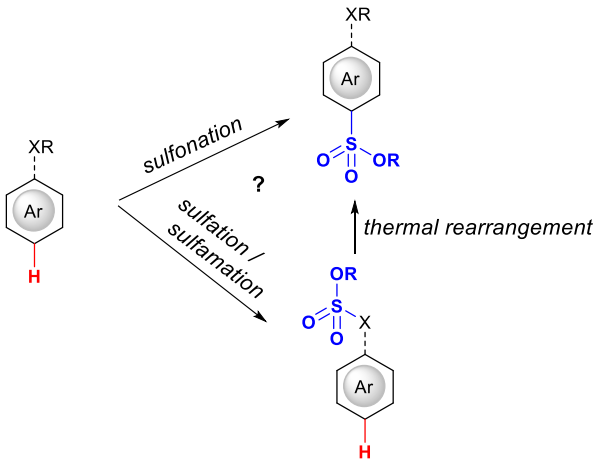


Abstract

The *C*(sp²)-aryl sulfonate functional group is widely found in bioactive scaffolds but can often only be accessed under forcing temperatures (>190 °C) and corrosive reaction conditions. Inspired by the Tyrer process to sulfa dyes that involves an aniline *N*(sp²)-SO_3 intermediate *en route* to a *C*(sp²)-SO_3 rearranged product - we deployed tributylsulfoammonium betaine (TBSAB) as an initiating mild sulfamating agent to sulfonate relay reagent.

A range of aniline and heterocyclic scaffolds were sulfonated in high conversions (6 examples of *N*(sp²)-sulfamates up to 99% isolated yield and 16 examples of C(sp2)-sulfonate in up to 80% isolated yield) with the ability to change the *ortho-para* selectivity of the products obtained under thermal control. Isolation of the *N*(sp²)-SO_3 intermediates for a two-step procedure was significantly lower yielding than a direct one-pot procedure.

Furthermore, we explore counterion effects on the *N*- to *C*- sulfate rearrangement and discovered the reversibility of the TBSAB reagent. Investigation of the *N*- to *C*- mechanism through designed examples with variation at the heteroatom position, and kinetic isotope experiments ($KIE^{H/D}$) confirmed the formation of a key *N*(sp²)-SO_3 intermediate and further supporting evidence of an *inter*molecular mechanism. Compounds without an accessible nitrogen (or hydroxyl) lone pair did not undergo sulfonation under these reaction conditions.

Keywords

Sulfation; sulfonation; sulfamation; rearrangement

Introduction

Sulfamated (*N*(sp²)-SO_3) and sulfonated (*C*(sp²)-SO_3) arylated motifs are found in a variety of valuable commodities including sulfa dyes, sulfa drugs and bioactive molecules (**Figure 1**).

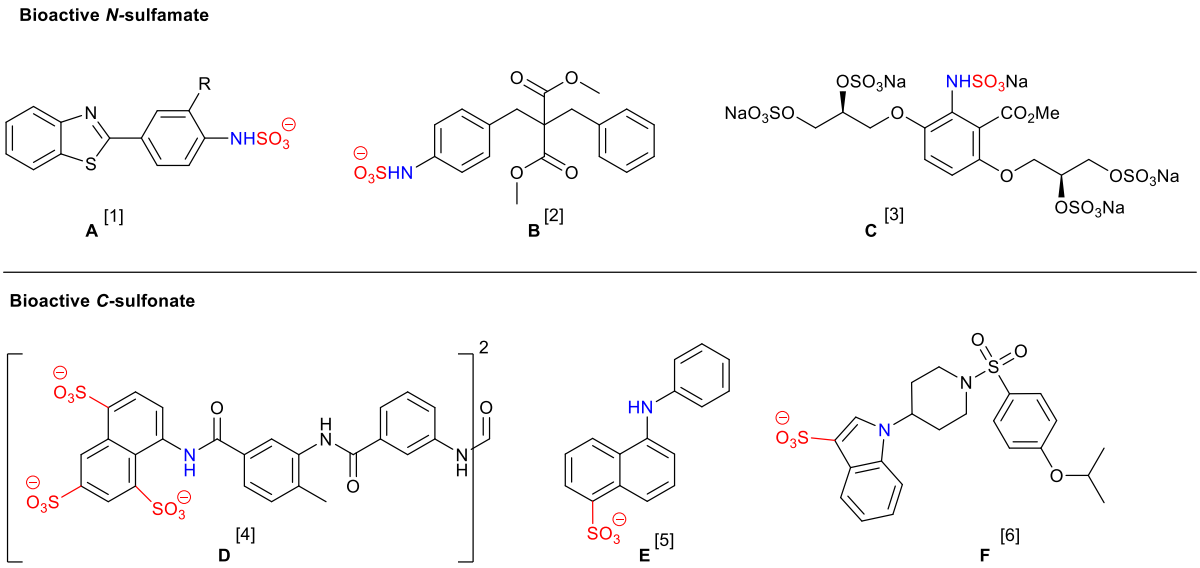


Figure 1. Structures of bioactive sulfamated and sulfonated molecules.

Examples of bioactive *N*(sp²)-sulfamates include A) a sulfamate salt prodrug derivative of the potent and selective 2-(4-aminophenyl)benzothiazole anti-cancer agent; [1] B) a malonate templated sulfamic acid phosphotyrosine mimetic as a selective and potent inhibitor of HPTPβ (a protein tyrosine phosphatase); [2] C) a glycomimetic that has protective effects against lipid-induced endothelial dysfunction, restorative effects on diabetic endothelial colony forming cells, and preventative effects on downstream vascular calcification. [3] Examples of bioactive *C*(sp²)-sulfonates include: D) suramin, an approved medication for treating river blindness and African sleeping sickness; [4] E) an inhibitor against coenzyme A binding site of choline acetyltransferase [5] and F) an indole derivative possessing PGD2 receptor antagonist activity. [6]

Furthermore, the mechanism by which sulfur trioxide (SO_3) is transferred in a S_EAr reaction to afford these type of aryl *C*(sp²)-sulfonate has been of perennial interest and reinvestigated by several groups. [7-19]

In turn, methods to prepare these *N*(sp²)-sulfamated precursors are limited [20-24] and *C*(sp²)-sulfonated compounds are often only achievable under more forcing conditions (**Chart 1**). [25-29] An *ortho*-selective aminative rearrangement of (arenesulfonyl)hydroxylamines has recently been revealed. [30]

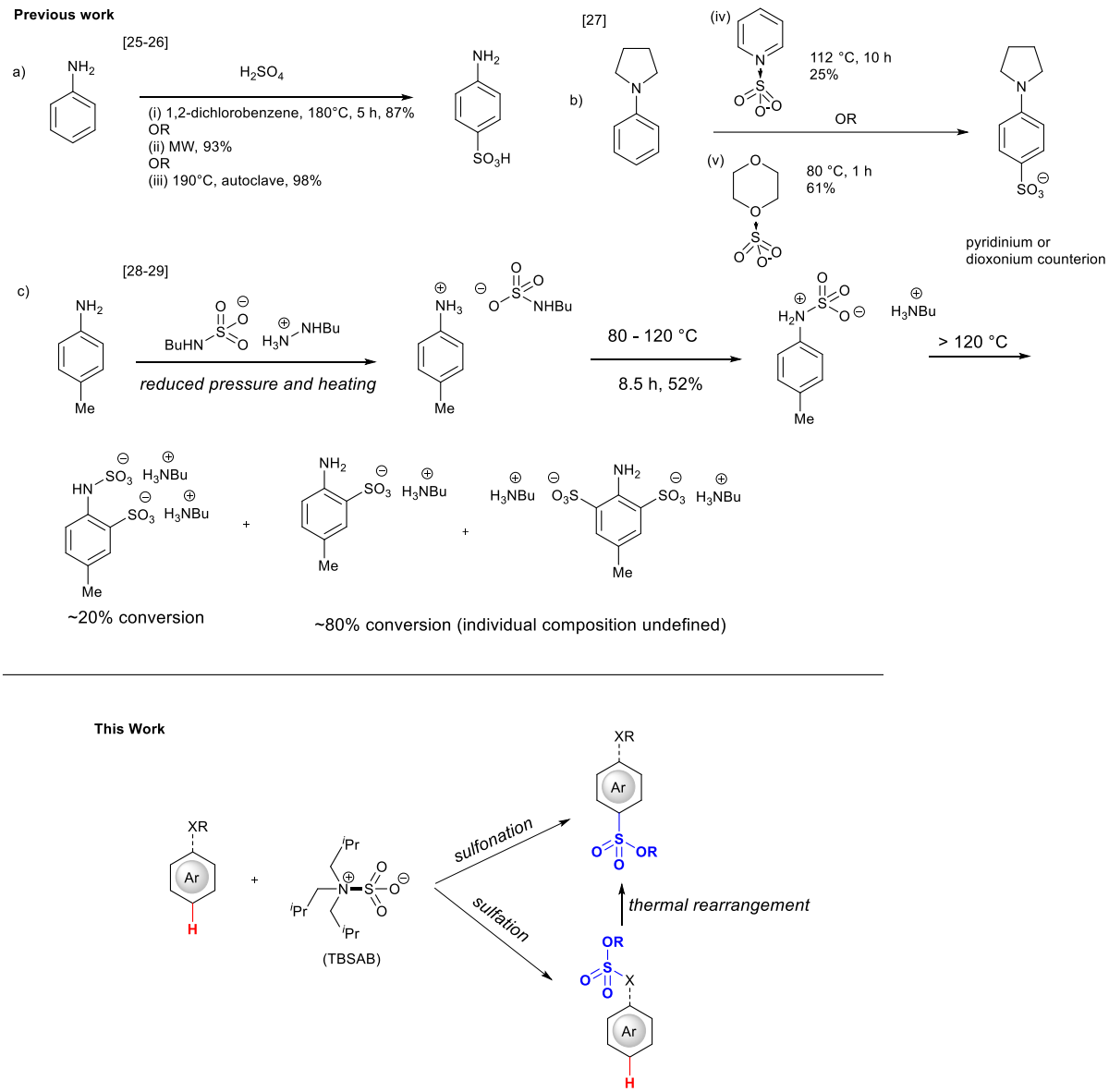
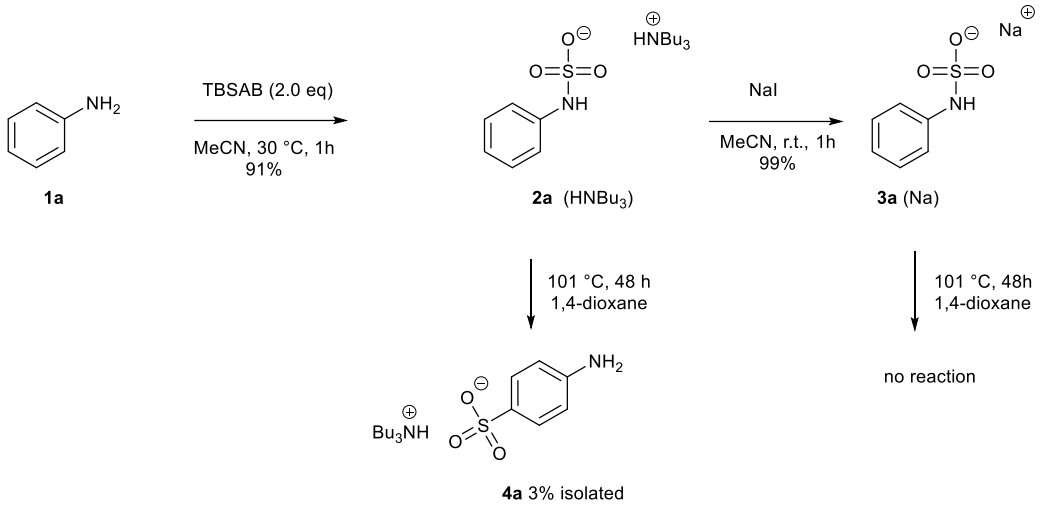


Chart 1. *Previous Approaches* towards the synthesis of *p*-aminobenzene sulfonic acid compounds using an *N*- to *C*-SO_3 transfer and *This Work*: using TBSAB to introduce SO_3 group into aromatic systems.

Inspired by the Tyrer process to *C*(sp²)-sulfonated aryl systems and the potential intermediacy of an *N*(sp²)-arylsulfamate, [31-36] we considered whether the mild sulfating reagent: tributylsulfoammonium betaine (TBSAB), [37-38] would give rise to different reactivity profiles, chemoselectivity or regioselectivity due to the *N*-tributyl ammonium counterion [39-41] or a more convenient preparation to C-sulfonated molecules.

Results and Discussion

Our initial investigations focussed on preparing the anticipated key *N*(sp2)-aniline sulfamate as both the tributylammonium and sodium salts to explore whether there are any counterion differences (**Scheme 1**).



Scheme 1. Initial attempts to prepare aniline sulfamates as their tributylammonium and sodium salts and resulting thermal rearrangement products.

Following a single reported example of aniline sulfamation, [20] we were able to prepare **2a** in 91% yield as its tributylammonium salt (**Scheme 1**). Treatment of **2a** with sodium iodide afforded the corresponding sodium salt, **3a** in quantitative yield. Refluxing **2a** and **3a** in 1,4-dioxane, a trace (3% isolated) *para*-rearrangement product (**4a**) with the tributylammonium counterion and no rearrangement with the sodium counterion. Thus, indicating the suitability of the tributylammonium counterion for further exploration.

To probe the rearrangement ability of the aniline core a range of *N*(sp²)-sulfamated anilines were synthesised using TBSAB as a mild sulfamating agent (**Chart 2**) in 95-99% conversions and 70-99% isolated yield. The 2,6-dichloroaniline example (**2g**) proved recalcitrant to undergoing sulfamation under these conditions. Examples selected varied the steric bulk around the aniline nitrogen from hydrogen < methyl < ethyl < isopropyl. At this stage to avoid the complexity of simultaneous *ortho* product formation both *ortho* position were blocked except for **2c**.

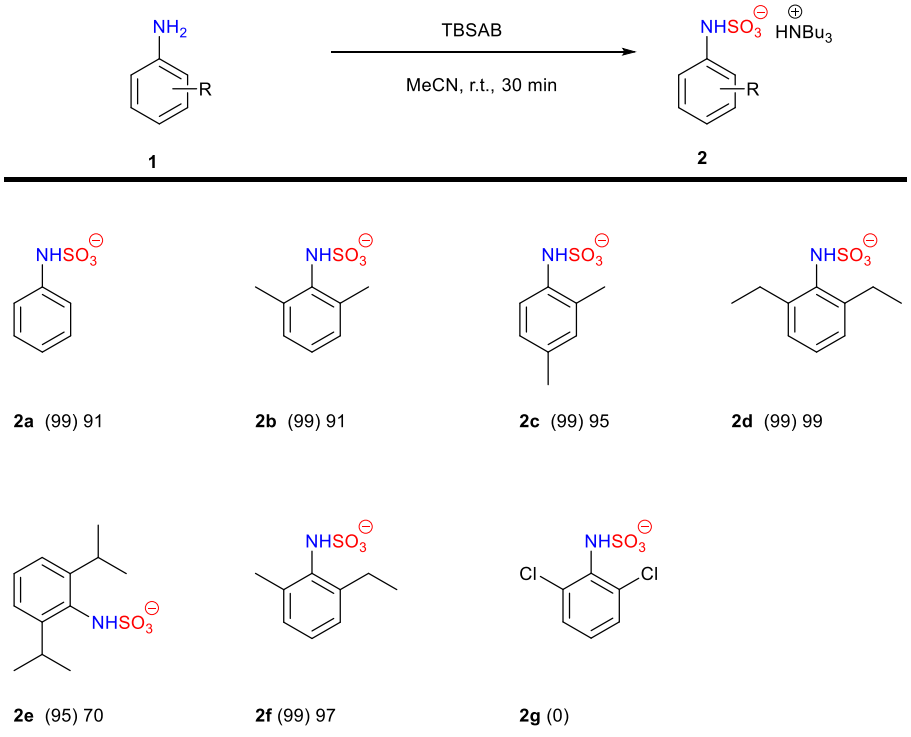


Chart 2. Synthesis of *N*(sp²)-anilino sulfamates using TBSAB. The tributylammonium cation is omitted for clarity.

Thermal treatment of the successful sulfamated anilines (**2**) under reflux [34] led to low to modest conversions of the sulfonated product (**Chart 3**). All structures where the *para* site was accessible afforded an isolable (3-24% yield) of the *para*-sulfonated product. The *ortho* accessible analogue (**4c**) did not form under these conditions despite similar electron rich electronics to **4b**. Instead, under these conditions we were able to regenerate TBSAB and aniline, demonstrating the reversibility of this reagent for the first time.

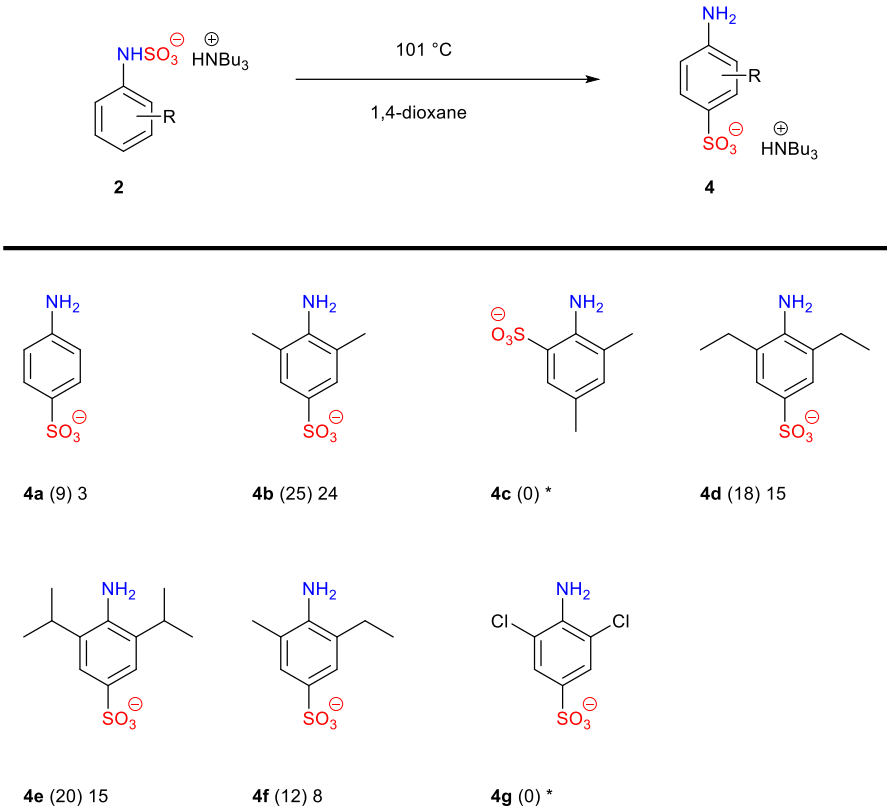
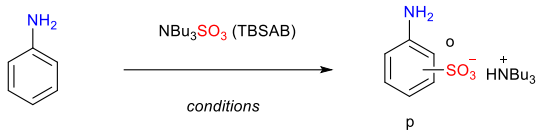


Chart 3. Initial attempts to access 4-aminobenzene sulfonate compounds by thermal rearrangement of **2**.

These results (**4b**, **4d**, **4e**, **4f**) where both *ortho* sites are blocked agree with both the Illuminati [34] and Spillane [35-36] stepwise *inter*molecular mechanism - as an *ortho-para* sulfate walk is not possible. Due to the non-isolation of **2g** (**Chart 2**), **4g** could not be generated in a stepwise manner, we decided to react 2,6-chloroaniline directly with TBSAB and reflux in a one-pot set-up, a low conversion 7% and 5% isolated yield of **4g** was found suggesting challenging sterically demanding and electron withdrawing examples could be prepared in one-pot and may also improve other lower yielding examples. We thus screened one-pot conditions for the direct reaction of anilines with TBSAB and *in situ* thermal rearrangement (**Chart 4**).



1a 4a

Entry	Eq.	T [°C]	Atmosphere	Solvent	Conversion (*p*) at 2 h (%)	Conversion at 24 h (*p*) (%)	Selectivity (*p* :*o*)
1	0.5	101	Ar	1,4-Dioxane	6	7	-
2	1	101	Ar	1,4-Dioxane	1	6	-
3	1.5	101	Ar	1,4-Dioxane	7	10	-
4	2	101	Ar	1,4-Dioxane	4	12	-
5	4	101	Ar	1,4-Dioxane	4	9	-
6	2	101	Air	1,4-Dioxane	3	11	-
7[b]	2	80	Ar	1,4-Dioxane	-	-	-
8	2	101	Ar	Formic acid	-	-	-
9	2	101	Ar	2-Butanol	-	-	-
10	2	80	Ar	DMF	-	-	-
11	2	101	Ar	DMF	4	13	-
12	2	120	Ar	DMF	32	58	>10:1
13	2	140	Ar	DMF	30	49	5:1
14	2	120	Ar	DMSO	25	48	8:1
15	2	140	Ar	DMSO	15	35	2:1
16[c]	2	160	Ar	DMSO	-	-	-
17[c]	2	180	Ar	DMSO	-	-	-
18	2	120	Ar	1,2-dichlorobenzene	27	52	>10:1
19	2	140	Ar	1,2-dichlorobenzene	20	44	4:1
20[c]	2	160	Ar	1,2-dichlorobenzene	-	-	-
21[c]	2	180	Ar	1,2-dichlorobenzene	-	-	-

Chart 4. Optimisation of a model system. [a]Conversion and selectivity were determined by ^{1}H NMR spectroscopy; [b]No reaction occurs below 80 °C; [c]Compounds began to decompose above 160 °C

Entries 1-6 (**Chart 4**) varied the equivalents of TBSAB, the highest conversion was observed with 2.0 equivalents (entry 4). Entry 7 (**Chart 4**) shows that an inert atmosphere is essential to the reaction. The use of polar protic solvents led to the unwanted breakdown of the *N*(sp^2)-sulfamate to the aniline starting material (**Chart 4**, entries 8 and 9). This was confirmed *via* treatment of an authentic sample of the sulfamate.

Entries 10-13 (**Chart 4**) detail the use of DMF as the solvent and varying the reaction temperature. With increasing temperature higher conversions were found with an optimum at 120 °C (entry 12). Higher temperatures (> 120 °C) were found to lead to more *ortho*-substituted product e.g., selectivity (*para* : *ortho*) decreases from 10 : 1 to 5 : 1. Entries 14-17 (**Chart 4**) detail the use of DMSO as the solvent. Although entry 14 was comparable to the optimal DMF result, complications of removing DMSO led to this being discontinued. Entries 18-21 (**Chart 4**) detail the use of 1,2-DCB as the solvent. Similarly, entry 18 was comparable and gave a slightly better *para* : *ortho* ratio than DMF (entry 12), but difficulties removing a high b.p. solvent ruled out further investigation.

Furthermore, in both the DMSO and 1,2-DCB examples evidence for the degradation of TBSAB was found above 160 °C. With the optimal conditions for a one-pot *para*-selective S$_E$Ar identified a screen of variously substituted anilines (probing sterics and electronics), heterocycles and oxygen containing systems were screened (**Chart 5**).

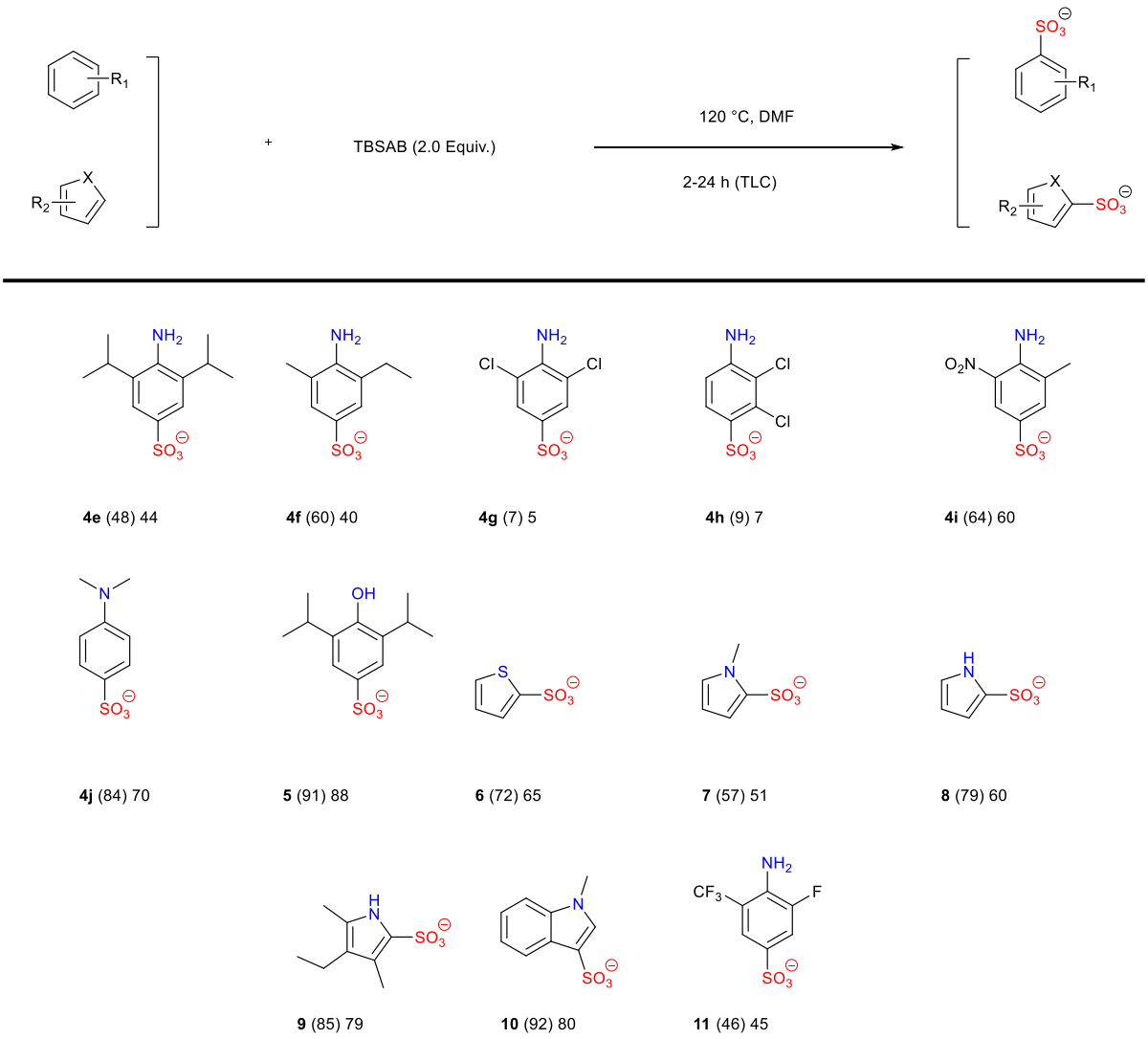


Chart 5. Reaction scope on diverse aromatic ring systems in one-pot reaction. The tributylammonium cation is omitted for clarity.

The one-pot method applied to compounds **4e**, **4f** and **4g** (**Chart 5**) resulted in dramatic improvements in conversion and isolated yield compared to the step wise procedure (**Charts 2-3**). **4e** increased from a linear 11% yield to 44%, **4f** increased from a linear 18% yield to 40%, and **4g** increased from no reaction to 5% isolated yield. A regioisomer of **4g** gave a similar low yield of 7% (**4h**) demonstrating the deactivating effect of the di-chloro-aryl ring system. However, other electron withdrawing groups are well tolerated. The nitro containing example (**4i**) proceeded in a modest 64% conversion (60% isolated). *N*,*N*-dimethylaniline proceeded smoothly to afford the *para*-substituted sulfonate in 70% isolated yield (**4j**). Moving to other heteroatoms, the hydroxyl group of the sterically demanding anaesthetic, propofol, was readily sulfonated in an 88% isolated yield (**5**). Thiophene was readily sulfonated in the 2-position (**6**) in a 65% yield, protected (**7**) and unprotected pyrroles (**8**) were sulfonated in 51 and 60% yields respectively. A tetrasubstituted pyrrole (**9**) was prepared in an excellent 79% yield and *N*-methylindole (**10**) was sulfonated at the C3 position with an 80% isolated yield. Furthermore, a fluorine containing building block was readily sulfonated in 45% isolated yield (**11**). In turn these sulfonated (hetero)aryl systems can be further manipulated to sulfonyl chlorides, sulfonamides, and sulfinates as building blocks in medchem. [30]

Control experiments

The mechanism of the sulfamate-sulfonate process has been well studied and shown conclusively to proceed *via inter*molecular rearrangement by Spillane using a ^{35}S labelling experiment. [35-36] However, a question remained as to whether an *N*-sulfamate is indeed necessary for the reaction to proceed (**Chart 6**).

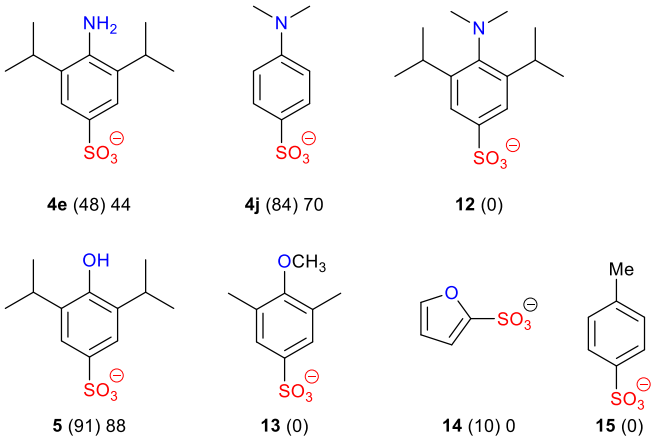


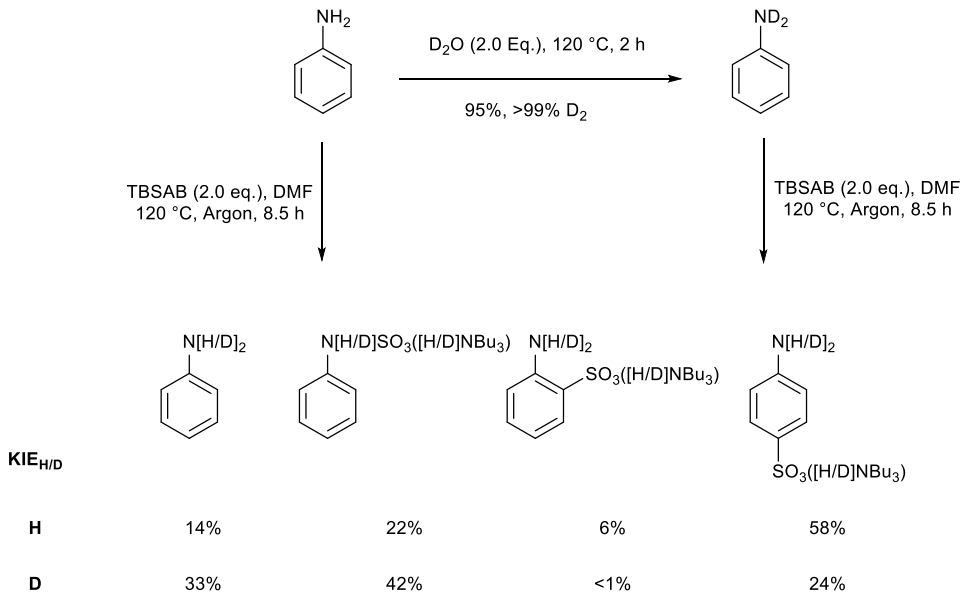
Chart 6. Control experiment results.

N,*N*-Dimethylaniline proceeded smoothly to afford the para-sulfonate **4j** in a 70% isolated yield (84% conversion). The equivalent *N*,*N*-dimethylamine-propofol analogue to **5** is **12** did not show any evidence of reaction by crude ^{1}H NMR spectroscopy. A molecular model demonstrated how sterically compressed the sulfamate would be sandwiched between a di-*ortho*-isopropyl groups. [42] Thus, sulfamation is necessary prior to sulfonation.

Replacing the phenol in the propofol example (**5**, 91% conversion (88% isolated), with a similar but less sterically demanding methoxy example (**13**) resulted in only trace conversion to the *para*-sulfonated **13** (by time course ^{1}H NMR spectroscopy). The need for an available hydroxyl group can be further ascribed from the results of **14**. A range of conditions were applied (r.t to 85 °C) and solvents (DCM, MeCN, and 1,2-DCE) at best at ~10% conversion was found. Isolation of the sulfated furan was further complicated by the presence of residual TBSAB (23% w/w purity by ^{1}H NMR spectroscopy).

To probe whether sulfonation of the aryl system is possible without a heteroatom, toluene was treated under the standard conditions (TBSAB, 120 °C, DMF, 24 h) and no trace of **15** was observed in the crude sample by ^{1}H NMR spectroscopy.

To further prove the requirement for *N*-sulfamation to occur prior to sulfonation as kinetic isotope experiment was devised (**Scheme 2**). The conversion of both rearrangement and sulfamate intermediate products noticeably decreased which implies the rate-determining step of this reaction is formation of the *N*-sulfamate.



Scheme 2. KIE$^{(H/D)}$ effects on aniline sulfamation/sulfonation.

Conclusions

In this study we have demonstrated that TBSAB is an efficient aniline *N*-sulfamation reagent and mild sulfamate to sulfonate relay reagent. A range of aniline and heterocyclic scaffolds were sulfonated in high conversions (6 examples of *N*(sp^2)-sulfamates up to 99% isolated yield and 16 examples of *C*(sp^2)-sulfonate in up to 80% isolated yield) with the ability to change the *ortho-para* ratio of the products obtained under thermal control. A re-investigation of the *N*- to *C*- sulfate rearrangement mechanism through designed examples with variation at the heteroatom position, and kinetic isotope experiments (KIE$^{H/D}$) confirmed the necessity of an *N*-sulfamate intermediate.

Supporting Information

See supporting information for characterization data on all compounds and accompanying ^{1}H, ^{13}C and ^{19}F NMR spectra.

Author Contributions

AMJ conceived the project, supervised, and drafted, revised the manuscript. YZ conducted the experiments and drafted the manuscript. All authors agree to the final version.

Conflicts of interest

There are no conflicts to declare.

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