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A new synthetic route to aryl hydroxysulfonamides via a novel Fries-type rearrangement of aryl *N*,*N*-dialkylsulfamates

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Abstract—A novel thia-Fries rearrangement of sulfamates **1** in $AlCl_3$ giving good yields of *para*-**2** and *ortho*-**3** arylhydroxysulfonamides offers a new and efficient route to these sulfonamides.

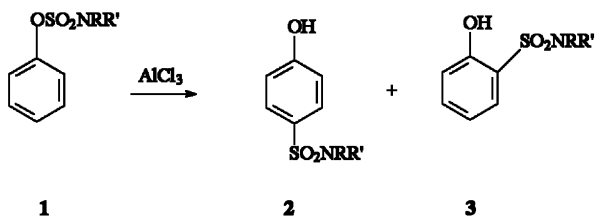
In this communication, we report a novel thia-Fries rearrangement (Scheme 1) in which a series of ten aryl *N*,*N*-dialkylsulfamates **1** have been isomerised to *para*-**2** and/or *ortho*-**3**-hydroxysulfonamides in good yields (Table 1). This is a new and efficient method for synthesising sulfonamides bearing an -OH functionality.

Since the original report of Rittler[1] of the Fries rearrangement giving hydroxydiarylsulfones, there have been numerous literature references to this rearrangement[2a–d] and the majority of these deal with the rearrangement of arylsulfonates, $PhSO_2OPh$ to sulfones, $HOC_6H_4SO_2Ph$.

In Table 1 in runs 1–3 good yields of *ortho*- and *para*-sulfonamides were obtained. In runs 4 and 6–9, where the *para*-position is blocked, only *ortho*-sulfonamide product was obtained. In runs 5 and 10 (both *ortho*-positions are blocked) only *para*-sulfonamide product was recovered.

When 2,4,6-trichlorophenyl *N*,*N*-dimethylsulfamate was subjected to the rearrangement conditions it did not react and no trace of the *meta*-hydroxysulfonamide was found. Where comparison is possible, yields of sulfonamide product(s) in this present rearrangement are comparable to or generally better than those reported in alternative syntheses.[3–9] Further, the rearrangement appears to offer a short and convenient route to sulfonamides from certain medicinally important steroidal sulfamate esters.[10]

The *ortho*/*para* ratio in the rearrangement has been explored for **1** ($R^1=R^2=Me$) under varying conditions (Table 2). Shorter reaction times and lower temperatures seem to favour the *ortho*-isomer; at temperatures of $\geq 120°C$ the *ortho*/*para* ratio is fairly constant except at 140°C when it is maximised after 10–15 min of reaction We have established that the two sulfonamides isolated are very stable and do not rearrange when heated over a range of 60–150°C in $AlCl_3$. An almost quantitative product balance was achieved between



1 **2** **3**

Scheme 1.

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Table 1. Rearrangement[a] of sulfamate esters to arylhydroxysulfonamides in $AlCl_3$ at 140°C for 1 h

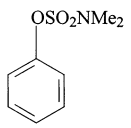
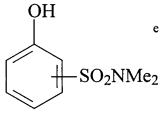
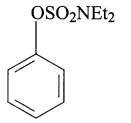
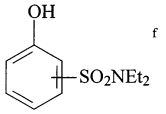
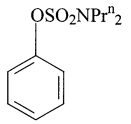
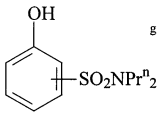
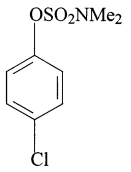
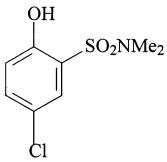
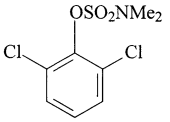
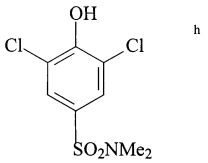
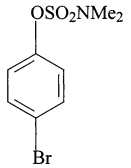
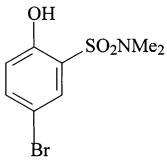
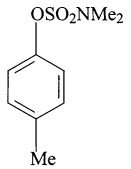
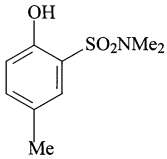
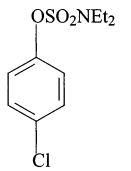
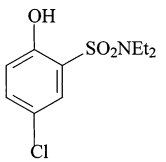
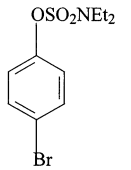
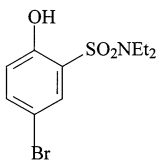
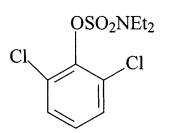
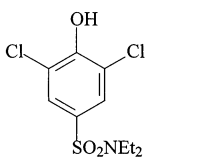
Run	Sulfamate ester[b]	Sulfonamide[c] Products	Yield (%)
1		 [e]	88 (0.5)[d]
2		 [f]	78 (1.6)[f]
3		 [g]	77 (1.7)[g]
4			69
5		 [h]	76
6			72
7			49
8			67
9			86
10			69

Table 2. *ortho*/*para* Ratio obtained in the rearrangement[a] of sulfamate ester **1** ($R^1 = R^2 = Me$) in $AlCl_3$ at various temperatures and times

Temp. (°C)	*ortho*/*para* Time (min)				
	5	10	15	30	60
90	2.7	1.3	1.1	1.3	0.7
100	1.2	1.2	0.8	0.9	0.7
110	1.2	1.1	0.6	0.7	0.6
120	0.6	0.6	0.5	0.4	0.5
130	0.5	0.5	0.5	0.5	0.5
140	0.5	1.0	0.9	0.5	0.5

[a] Using 0.5 g ester and a 1:1 molar ratio of ester to $AlCl_3$. The various temperatures (±5°C) were maintained in an oil bath. Detection of isomers was by reversed-phase HPLC.

ester and product(s) though at higher temperatures some decomposition to parent phenol ($\leq 10\%$) was noted.

Crossover experiments to explore the molecularity of the rearrangement are in hand using nitrobenzene as solvent. Further work is in progress to maximise yields, to probe other effects, e.g. varying catalyst, solvent etc. and to attempt the rearrangement of sulfamates of the type $ArOSO_2NH_2$ which, if successful, could provide a route to many medicinally important sulfonamides.

[a] Using 0.5 g ester and a 1:1 molar ratio of ester to $AlCl_3$. An oil bath at 140±5°C was used for the reaction. The reaction was quenched with HCl and after extraction with CH_2Cl_2 product(s) were separated by column chromatography (silica gel) or by distillation under reduced pressure. [b] These were prepared by a standard method involving reaction of the appropriate sulfamoyl halide with the appropriate phenol giving generally ~70% yields. All gave good C, H and N microanalysis (within ±0.5%) except the sulfamate used in run 9 which had % C 38.96 (found); requires 39.52%. ^1H and ^{13}C NMR and MS were obtained for all esters. Esters used in runs 1, 4, 7, and 8 and the 2,4,6-trichloro ester (Ref. 4) and in run 2 (Ref. 5) have been reported previously and the mp's/bp's obtained are in agreement with reported values. [c] The sulfonamides all gave C, H and N microanalysis (within ±0.5%) except the products in run 7, which had % C 50.23 (found); requires 51.58% and % N 6.51, requires 5.96% and in run 9 which had % C 38.96 (found); requires 39.93%. ^1H and ^{13}C NMR and MS were obtained for all thirteen sulfonamides prepared. [d] The *ortho*/*para* ratio is given in parentheses for runs 1–3. [e] The *ortho*-hydroxy compound, mp 91–92°C (lit.[6] 67–70°C) was synthesised by an alternative route by us and gave a material with mp 91–92.5°C. The MS of the two compounds made by us were identical. The *para*-hydroxy compound had a mp of 97–98°C (lit.[7] 95°C; lit.[8] 94°C; lit.[9] 95–96°C). [f] The *para*-hydroxy compound, mp 94.5–95.5°C (lit.[6] 68–70°C; lit.[10] 49–50°C) was synthesised by an alternative route by us and gave a material with mp 94.5–95.5°C. The MS of the two compounds made by us were identical. [g] The *para*-hydroxy compound had a mp of 100–102°C (lit.[6] 102–104°C). [h] The product shown mp 162–165°C (lit.[11] 160–165°C; lit.[12] 137–138°C) gave ^1H and ^{13}C NMR and MS spectra which were consistent with the structure shown.

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