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LETTERS

Practical acid-catalyzed acylation of sulfonamides with carboxylic acid anhydrides

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Abstract—A highly efficient reaction between sterically and electronically diverse sulfonamides and carboxylic acid anhydrides to furnish monoacylated *N*-acylsulfonamides is described. This represents the first systematic disclosure of the scope of sulfuric acid-catalyzed acylation of sulfonamides. © 2003 Elsevier Science Ltd. All rights reserved.

The *N*-acyl sulfonamide moiety is a common structural motif in organic synthesis. Several recent developmental drugs including therapeutic agents for Alzheimer's disease,[1] inhibitors of tRNA synthetases as antibacterial agents,[2] and prostaglandin F1a sulfonamides for the potential treatments for osteoporosis[3] incorporate this functionality. In addition several *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl) methanesulfonamides have been employed as chemoselective *N*-acylating reagents.[4a]

The vast majority of reports that start from the parent sulfonamides describe the preparation of *N*-acyl derivatives by means of basic reaction media. For instance, the target compounds have been obtained by coupling of sulfonamides with acid chlorides or anhydrides using trialkylamines or pyridine[4a,b] or alternatively with alkali hydroxides.[4c–e] Another approach utilizes carboxylic acids along with coupling agents (e.g. EDC, DCC, or carbonyldiimidazole),[2,3] which must then be removed from the reaction mixtures. The less common reports mentioning this transformation under acidic conditions do not systematically examine the scope and limitations of the reaction. These reports give examples of reactions that are typically carried out on relatively small scale (<1 g) and without solvent, one example using a 'few drops' of H_2SO_4 in the carboxylic acid anhydride as reaction solvent.[5] During our efforts to develop a practical process for the synthesis of a recent clinical candidate at *GlaxoSmithKline*, we were challenged with the conversion of an aryl sulfonamide to its propionate derivative. We needed a method that would provide consistently high yield and purity and could be conducted on a large scale. We were reluctant to employ basic reaction conditions due to our substrate's lack of stability in basic reaction conditions. In addition we found that conditions required to fully acylate the suylfonamide using conventional base catalyzed methods (treatment with 1.5 equivalents of propionic anhydride and 1.05 equivalents of 4-DMAP in CH_2Cl_2) gave rise to the bis-acylated byproduct (up to 4% by HPLC), which proved difficult to remove. It was for these reasons that we turned our attention to acid catalyzed reaction systems. An initial screen was conducted using all possible combinations of three solvents (CH_3CN, EtOAc, and THF) and three acid catalysts (96% sulfuric acid, 4N HCl/dioxane and 30% HBr in $PrCO_2H$) at 60°C. Surprisingly, only sulfuric acid in combination with CH_3CN resulted in a highly efficient transformation (>95% product by HPLC). With the exception of 5% sulfuric acid and EtOAc (36.7% product after 4 h), all other acid–solvent combinations produced less than 2% product by HPLC after 4 h. These results can be attributed to the solvent's ability to stabilize the acylium intermediate as well as the pK_a of the solvents used in comparison to that of the anhydride. If the equilibrium favors protonation of the solvent then the reaction cannot progress. This is further evidenced by the fact that we observed that small amounts of acetone also inhibit the reaction. Based on these observations, we developed a process in which the sulfonamide, sus-

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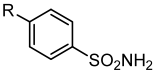
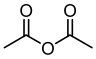
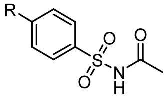
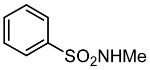
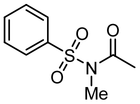
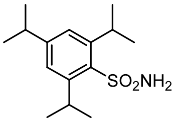
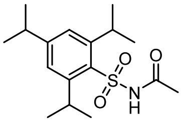
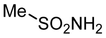
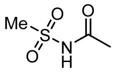
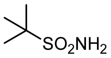
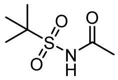
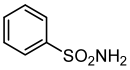
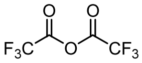
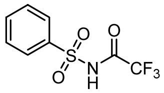
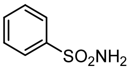
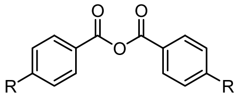
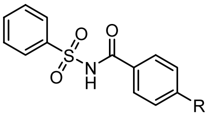
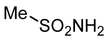
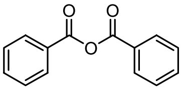
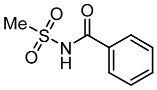
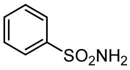
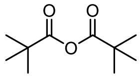
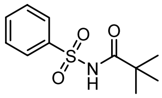
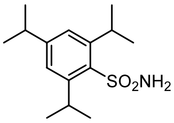
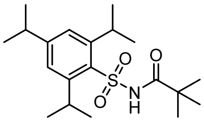
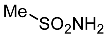
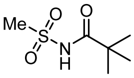
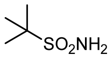
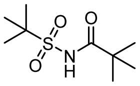
Table 1. Synthesis of *N*-acylsulfonamides[a]

Entry	Sulfonamide	Carboxylic Acid Anhydride	*N*-Acylsulfonamide	Isolated Yield (%)
1				a) R=H; 95 b) R=OMe; 91 c) R=NO_2; 98
2				96[d]
3				90
4				92
5				86
6				60
7				a) R=H; 77 b) R=CF_3; NR c) R=OMe; NR
8				44
9				94
10				90
11				94
12				61[b,c]

[a] Reaction carried out in 10 Vol CH_3CN using 3 mol% H_2SO_4 at 60 °C.

[b] Reaction stalled at 73% conversion.

[c] Isolated by flash column chromatography.

pended in acetonitrile, is treated with propionic anhydride (3 equivalents) and catalytic concentrated H_2SO_4 (2 mol%) at 60°C to provide the mono-acylated product in excellent yield.

Since no systematic study regarding this transformation has been published to date, we were interested in applying this practical method to a set of sterically and electronically diverse anhydrides and sulfonamides in order to provide a general method of entry into the acylated sulfonamides. As demonstrated in Table 1, the reaction is generally high yielding and worked on most substrates attempted. The *p*-triflouromethyl substituted benzoic anhydride provided no significant reactivity, presumably due to its inability to form the activated acyllium ion under these conditions. It should also be noted that the *p*-methoxy benzoic anhydride was also unproductive using this protocol presumably due to the ability of the methoxy ether to preferentially protonate thus effectively preventing the acid from activating the anhydride. Generally the steric bulk or electronic nature of the sulfonamid had little effect on the efficiency of the process.

In conclusion, we have presented a general method for the synthesis of *N*-acylsulfonamides from sterically and electronically diverse aliphatic and aromatic substrates, which should render it valuable for widespread application. All new compounds described gave satisfactory spectral and analytical data.[6]

Typical procedure: Under a nitrogen atmosphere a solution of benzenesulfonamide (2.0 g, 12.7 mmol) and acetic anhydride (1.95 g, 19.1 mmol) in acetonitrile (20 ml) was stirred at 60°C and treated with 96% sulfuric acid (38.8 mg, 3 mol%). The solution was maintained at 60°C for 40 min until reaction was judged complete by TLC or HPLC. The solvent was removed by distillation to achieve a total volume of 8 ml and then the solution was cooled to 20°C. Water (10–15 ml) was added dropwise to form a precipitate. The resulting mixture was stirred for 1 h at 20°C and then filtered. The crude solid was washed with water (5–10 ml) and then dried in vacuo under nitrogen at 50°C for 18 h. Weight of white crystalline solid was 2.40 g, 95%.

Acknowledgements

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6. ^{1}H, ^{13}C NMR and elemental analysis for key new compounds **3** and **5**:
   3: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.23 (s, 2H), 4.30–4.17 (m, 2H) 2.97–2.83 (m, 1H), 1.19 (m, 18H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.87, 152.95, 150.32, 132.29, 123.62, 33.35, 28.35, 24.31, 23.34, 22.91. Anal. calcd for $C_{17}H_{27}NO_3S$: C, 62.74; H, 8.36; N, 4.30; S, 9.85. Found: C, 62.87; H, 8.22; N, 4.40; S, 9.87.
   5: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.10 (s, 1H), 2.01 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.73, 60.75, 23.89, 23.79. Anal. calcd for $C_6H_{13}NO_3S$: C, 40.21; H, 7.31; N, 7.81; S, 17.89. Found: C, 40.12; H, 7.42; N, 7.86; S, 17.80.