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A Convenient Method for the Preparation of Acylsulfonamide Libraries

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Abstract: The preparation of an acylsulfonamide library is described using resin bound EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide). A polymer supported sulfonic acid (A-15) is used as a scavenger to remove dimethylaminopyridine and purification only involves filtration of the reaction mixture. This method provides the acylsulfonamides products in good yields and purity.

Solid-phase organic synthesis (SPOS) for the preparation of small molecule libraries is now routinely applied in pharmaceutical research for the discovery and optimization of lead compounds.[1-6] Polymer supported reagents have emerged as a complementary approach to SPOS.[6-9] In certain applications, supported reagents offer advantages over traditional solid phase synthesis since the substrate need not possess a suitable functional group to attach to the resin. Also, there are generally two additional steps required in SPOS, one to attach the substrate to the resin and the second to cleave the product from the solid support. With supported reagents the starting material and product remain in solution and the reactions can be monitored by standard methods (i.e. TLC, nmr, GC, HPLC). As part of our research, we were interested in preparing an acylsulfonamide library from a carboxylic acid intermediate. Acylsulfonamides are an interesting class of compounds in medicinal chemistry as they serve as carboxylic acid equivalents. The solution phase synthesis of is usually carried out by condensing carboxylic acids (RCO_2H) with sulfonamides (RSO_2NH_2) using dehydrating agents such as EDC or DCC with the add of excess dimethylaminopyridine (DMAP). The use of DMAP is required due to the low reactivity of the sulfonamide nucleophile. At the end of the reaction, the acylsulfonamide is obtained after an acidic workup to protonate the acylsulfonamide-DMAP salt. However, since this acid lacked an appropriate functional group to attach to a resin, we set out to investigate the use of polymer supported dehydrating agents for the preparation of acylsulfonamides.[10] We wish to report herein our work in the use of the previously reported polymer

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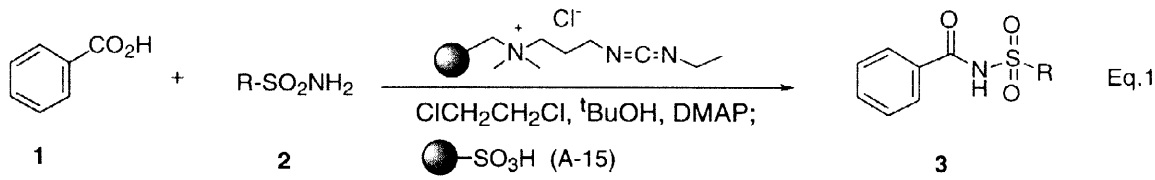
supported version of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (P-EDC) for the preparation of acylsulfonamide libraries.[11,12]

To adapt this reaction to a 'reverse' polymer supported version, we first set out to investigate if P-EDC (prepared by treating Merrifield's resin with EDC in DMF at 100 °C overnight) would induce the coupling of a carboxylic acid with a sulfonamide. We were pleased to observe that by simply treating 4-phenylbenzoic acid with 4-isopropybenzenesulfonamide, P-EDC and excess DMAP (5 equiv.) in $CHCl_3$, the desired acylsulfonamide was isolated after a standard aqueous acid workup. However, in order to make this a viable procedure for the generation of libraries, we required a convenient acidic workup to protonate the acylsulfonamide anion and a simple procedure to remove DMAP from the reaction mixture. Ideally, purification of these reactions would involve a simple filtration to remove the resin bound reagent and DMAP. We set out to investigate if treating the reaction mixture with a protic acid would precipitate DMAP from solution as its corresponding salt. A number of different acids were examined (CSA, TsOH, acetic acid, citric acid) but these failed to adequately remove DMAP from the reaction mixture. After some experimentation, we found that Amberlyst-15[13] (A-15, a commercially available solid supported sulfonic acid) served as a practical proton source to both protonate the acylsulfonamide and to remove DMAP from solution as its corresponding salt. With the use of A-15, generally greater than 95% of the DMAP was routinely removed from the reaction after filtration.

A variety of different solvents were examined in this reaction and it was found that a 1:1 mixture of $ClCH_2CH_2Cl$:^{t}BuOH served to provide the best yields of the coupled product. In initial experiments, one equivalent of the sulfonamide to carboxylic acid was used but after workup, the product was found to be contaminated with unreacted sulfonamide. This problem was alleviated by reducing the amount of the sulfonamide to 0.7 equivalents (relative to the carboxylic acid). The excess carboxylic acid remains bound to the resin and does not diminish product purity. The amount of resin was examined and the optimal quantity of P-EDC was found to be approximately 2.5 equivalents. Typically, 3 equivalents of DMAP are used in these reactions although in model experiments with benzoic acid, 2.5 equivalents of DMAP was found to be equally effective in promoting the condensation reaction. With these optimized conditions, benzoic acid **1** reacts with 4-isopropylbenzenesulfonamide **2** to give the corresponding acylsulfonamide **3** in 70% yield and 90% purity as determined by HPLC analysis (equation 1).

Having established reaction conditions for the 'reverse' solid phase synthesis of acylsulfonamides, the scope of this reaction was investigated using 25 sulfonamides.[14] **Table 1** summarizes the results of these reactions. Several points from this table are worthy of comment. Under the optimized conditions, the coupling reaction was found to be uniformly successful irrespective of the sulfonamide partner and the expected acylsulfonamides were furnished in good yields and purity. Inspection of the crude ^{1}H nmr spectra revealed that there was generally less than 5% of either DMAP or the starting sulfonamide present in the product. The coupling reaction proceeds well for both electron rich and electron poor benzenesulfonamides. In particular, it was gratifying to see that even the electron poor 4-nitrobenzenesulfonamide was efficiently condensed with benzoic acid to provide the expected product in good yield and purity (entry 8). Bulky substituents on the benzenesulfonamide do not interfere in the coupling reaction as is evident by

Table 1: Synthesis of Acylsulfonamide Library



1 2 3

Entry	Sulfonamide	Yield (%)[a]	Purity[b,c]
1	methanesulfonamide	66	85[d]
2	2-(carboxymethyl)-benzenesulfonamide	75	92
3	o-toluenesulfonamide	75	85
4	4-methoxybenzenesulfonamide	68	88
5	benzenesulfonamide	56	92
6	2-fluorobenzenesulfonamide	79	92
7	3-chlorobenzenesulfonamide	63	90
8	4-nitrobenzenesulfonamide	63	92
9	2-nitrobenzenesulfonamide	63	92
10	4-chlorobenzenesulfonamide	62	88
11	2,5 dimethylbenzenesulfonamide	76	92
12	2-chlorobenzenesulfonamide	81	88
13	pentafluorobenzenesulfonamide	73	88
14	2-chloro-6-methylbenzenesulfonamide	76	92
15	5-bromo-2-(aminosulfonyl)thiophene	57	90
16	2,5-dichlorobenzenesulfonamide	73	88
17	benzylsulfonamide	64	92
18	4-trifluoromethylbenzenesulfonamide	76	88
19	3-bromobenzenesulfonamide	68	86
20	2-phenylbenzenesulfonamide	73	91
21	2-trifluoromethylbenzenesulfonamide	63	91
22	3-methylbenzenesulfonamide	73	92
23	3,4,5-trichlorobenzenesulfonamide	74	90
24	2,4-dichlorobenzenesulfonamide	67	90
25	2,5-dimethoxybenzenesulfonamide	78	85

a) Yields refer to the isolated crude product. b) Purity of the acylsulfonamide was determined by HPLC analysis of the crude reaction product (uncorrected at 255 nm). c) All compounds gave satisfactory ^{1}H nmr and MS data. d) Purity determined by ^{1}H nmr spectra of the crude reaction product.

2-phenylbenzenesulfonamide in undergoing the acylation reaction (entry 20). It was observed, however, that if the reaction mixtures are not efficiently stirred, the product can be contaminated with as much as 40% of the starting sulfonamide.

In conclusion, acylsulfonamide libraries of benzoic acid have been prepared in good yields employing P-EDC as the dehydrating agent. The use of A-15 provides a quick and efficient means of removing DMAP from the reaction to provide the product in good purity.

References and Notes:

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[9] For a recent review on the use of functionalized polymers in organic synthesis see: Shuttleworth, S.J.; Allin, S.M.; Sharma, P.K. *Synthesis* **1997**, 1217 and references therein.

[10] A traceless linker approach can be used in this situation. This would, however, require additional synthetic efforts. Plunkett, M.J.; Ellman, J.A. *J. Org. Chem.* **1997**, *62*, 2885.

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[12] The polymer supported carbodiimide N-cyclohexylcarbodiimide N'-methylpolystyrene is now available from Novabiochem, catalog number 01-64-0211.

[13] Amberlyst-15 can be purchased from the Aldrich Chemical Company.

[14] General procedure: Into a 20 mL screw cap vial was added benzoic acid (50 mg, 0.41 mmol), $ClCH_2CH_2Cl$ (2.5 mL), tBuOH (2.5mL), DMAP (150 mg), P-EDC (650 mg) and the sulfonamide (0.29 mmol). The resulting mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was then diluted with 3-4 mL of EtOAc and approximately 1g of A-15 was added to the reaction. This mixture was allowed to stir for an additional 2 hours. At this time the reaction mixture was filtered through a short plug of silica gel (ca. 1 cm) through sintered glass funnel and the residue was rinsed with additional EtOAc. The resulting filtrate was concentrated to provide the acylsulfonamide product. Spectral data of acylsulfonamide for entry 2, Table 1. ^1H NMR (400 MHz, acetone-d_6) δ 10.8 (br s, 1H), 8.35 (m, 1H), 8.04 (m, 2H), 7.60-7.75 (m, 3H), 7.55 (m, 1H), 7.40-7.48 (m, 2H), 3.92 (s, 3H) ppm. LRMS found m/z 317.9 $(M-H)^+$, $C_{15}H_{12}NSO_5$ (M-H) requires 318.0. HPLC conditions: (A=0.5% $AcOH/H_2O$, B=CH_3CN). 0-5 minutes 75%A:25%B, 5-20 minutes linear gradient to 10%A:90%B; retention time of 11.8 minutes.