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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5181–5184

An expeditious and convenient synthesis of acylsulfonamides utilizing polymer-supported reagents

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Received 12 April 2007; revised 22 May 2007; accepted 25 May 2007
Available online 2 June 2007

Abstract—Acylsulfonamides can be rapidly and conveniently synthesized from a variety of carboxylic acids and sulfonamides utilizing the commercially available reagents, PS-DCC and DMAP under mild reaction conditions. DMAP can be efficiently scavenged by utilization of a silica-supported tosic acid cartridge (Si-SCX). In most of the cases studied, products with high purities and yields were obtained without the need for further purification.

N-Acylsulfonamides have been widely employed as carboxylic acid bioisosteres in medicinal chemistry due to their comparable acidity.[1] They offer the possibility for a wide range of structural modifications relative to the carboxylic acids themselves. As part of our ongoing program to develop efficient and robust methods for the preparation of biologically relevant compounds from readily available building blocks,[2] we sought to develop a convenient, expeditious, and high-yielding reaction protocol for the synthesis of acylsulfonamides, which would also be highly amenable to automation for the rapid generation of analogs.

In principle, acylation of sulfonamides can be accomplished by the reaction of sulfonamides with acids, anhydrides, esters, and acid chlorides. The direct condensation of carboxylic acids with sulfonamides is particularly attractive as a diverse array of carboxylic acids is commercially available. A number of synthetic procedures have been reported for the preparation of sulfonamides from acids using coupling reagents such as EDC, DCC, CDI or Mukaiyama's reagent.[1e,3] We have reported that amides can be effectively synthesized from carboxylic acids and amines using the PS-DCC/HOBt method under microwave heating.[2a] However, when this method was used for the synthesis of acylsulfonamide **1**, a very low conversion to the desired product **1** was indicated by crude LC/MS analysis (Table 1, entry 1). The conversion yield increased dramatically when HOBt was not added to the reaction (Table 1, entries 2 and 4). When the stronger base, 4-dimethylaminopyridine (DMAP), was used instead of DIEA, a quantitative conversion to the desired sulfonamide product was observed within 1 h as shown by crude LC/MS analysis (Table 1, entry 5). Inferior results were obtained when CH_3CN was used as the solvent instead of CH_2Cl_2 (Table 1, entry 6). Furthermore, we observed that the amount of reagents used could be scaled back dramatically. Eventually, it was found that with only 1.5 equiv of PS-DCC and 1 equiv of DMAP, the conversion to acylsulfonamide **1** was accomplished within 1 h with quantitative conversion (Table 1, entry 8).

Solid-phase extraction (SPE) techniques have proven to be useful for scavenging a wide range of excess reagents and reaction side-products. SPE is especially well suited for parallel synthesis since in many cases, a simple filtration will remove undesired materials, thereby greatly simplifying reaction workup. It has been found that the use of silica-supported reagents in SPE can greatly decrease the time required for byproduct sequestration.[4] Therefore, silica-bound *p*-toluene sulfonic acid (Si-SCX)[5] was studied for its effectiveness in scavenging DMAP, the base used in the acylsulfonamide synthesis. For these experiments, 0.8 mmol Si-SCX (1 g) was packed into a short column. A solution of the desired amount of DMAP in 1 ml of CH_2Cl_2 was passed through the Si-SCX cartridge by gravity filtration and washed with additional solvent. It was found that in this

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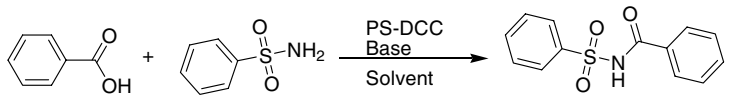
doi:10.1016/j.tetlet.2007.05.158

Table 1. Synthesis of acylsulfonamide **1** using PS-DCC/DMAP



1

Entry	PS-DCC (equiv)	Base (equiv)	HOBt (equiv)	Reaction condition	Conversion[a] (%)
1	3	DIEA (2)	1	MW, 110 °C, 10 min, CH_3CN	<10[b]
2	3	DIEA (2)	1	rt, 12 h, CH_2Cl_2	30[b]
3	3	DMAP (2)	1	rt, 12 h, CH_2Cl_2	35[b]
4	3	DIEA (2)		rt, 1 h, CH_2Cl_2	85
5	3	DMAP (2)		rt, 1 h, CH_2Cl_2	100
6	3	DMAP (2)		rt, 5 h, CH_3CN	40
7	2	DMAP (2)		rt, 1 h, CH_2Cl_2	100
8	1.5	DMAP (1)		rt, 1 h, CH_2Cl_2	100 (95)[c]

[a] Conversion based on crude LC/MS analysis.
[b] Other unidentified peaks were also observed.
[c] Isolated yield.

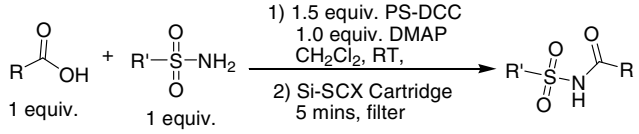
Table 2. Scavenging DMAP with an Si-SCX cartridge (1 g, 0.8 mmol loading)[6]

Entry	DMAP (mmol)	Washing solvent	DMAP collected after a single flow-through[b]
1	0.2	CH_2Cl_2[a]	None
2	0.2	CH_2Cl_2	None
3	0.2	MeOH	None
4	0.4	CH_2Cl_2	None
5	0.8	CH_2Cl_2	15%[c]

[a] The cartridge was pre-conditioned with CH_2Cl_2.
[b] Based on LC/MS analysis.
[c] Determined after drying down the filtrate.

case, pre-conditioning of the column with the solvent was not necessary (Table 2, entries 1 and 2). MeOH can also be used as the washing solvent if desired. This was particularly useful in cases where the crude product had poor solubility in CH_2Cl_2. In these cases, MeOH could be used to wash the cartridge to prevent the product from being precipitated. The sequestration process was very effective. DMAP (0.4 mmol) was scavenged completely when passed through a cartridge packed with 0.8 mmol Si-SCX in a single flow-though (Table 2, entry 4). This whole process took less than 5 min. Remarkably, when 0.8 mmol DMAP was used (1 equiv relative to the amount of Si-SCX on the cartridge in a

Table 3. Synthesis of acylsulfonamides from carboxylic acids and sulfonamides with PS-DCC/DMAP[7]



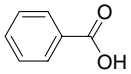
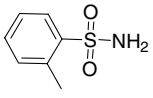
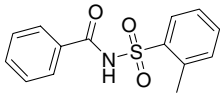
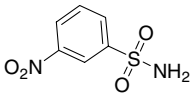
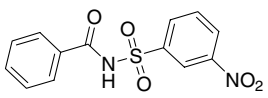
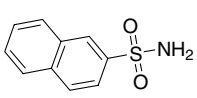
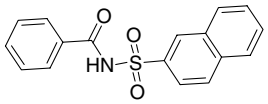
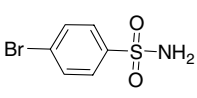
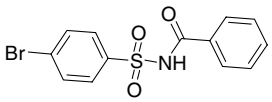
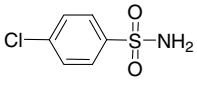
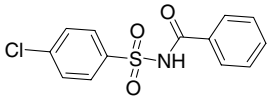
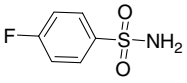
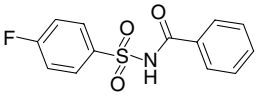
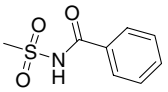
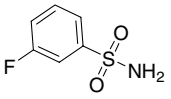
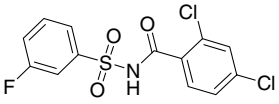
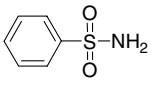
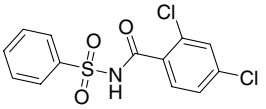
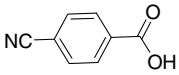
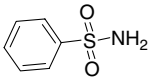
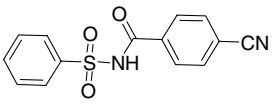
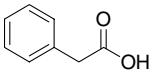
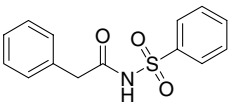
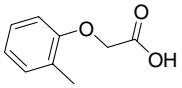
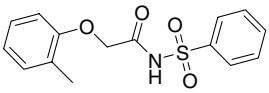
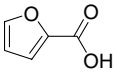
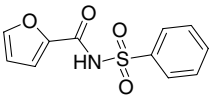
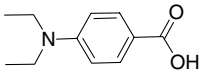
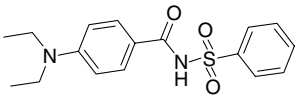
Entry	Acid	Sulfonamide	Product	Reaction time (h)	Conversion[a] (%)	Isolated yield (%)
1				1	100	99
2				1	100	98
3				1	100	100
4				1	100	97
5				1	100	90

Table 3 (*continued*)

Entry	Acid	Sulfonamide	Product	Reaction time (h)	Conversion[a] (%)	Isolated yield (%)
6				1	100	91
7				1	100	85
8				1	100	93
9				1	93	81[b]
10				1	100	85
11				1	100	92
12				1	100	86
13				1	100	94
14				8	100	87[c]

[a] Determined by crude LC/MS analysis and ^{1}H NMR analysis.
[b] Crude product was purified by reverse-phase HPLC.
[c] Crude material was purified by reverse-phase HPLC without filtering through a Si-SCX cartridge.

single flow-through), the Si-SCX cartridge was able to retain most of the material and only 15% DMAP was recovered from the filtrate (Table 2, entry 5).

Since the conversion to the acylsulfonamide **1** was quantitative under our conditions within 1 h, the crude material was directly loaded onto a Si-SCX cartridge and washed with additional CH_2Cl_2. The filtrate thus collected was free of DMAP as shown by LC/MS. After solvent evaporation, acylsulfonamide **1** was obtained in 95% isolated yield with high purity. No further purification was necessary.

With this convenient protocol in hand, we next examined the scope of this method, and the results are summarized in Table 3. Of note is that most of the reactions reported in Table 3 were completed within 1 h with quantitative conversion. In all cases studied but two (Table 3, entries 9 and 14), passing the crude mixture through a Si-SCX cartridge as described previously afforded the pure product without the need for further purification. This method was found to be quite general and worked well for a variety of alkyl and aryl carboxylic acids and sulfonamides. Notably, electron deficient sulfonamides worked just as well. It was found that basic groups are tolerated although longer reaction time was required and the Si-SCX cartridge could not be used (Table 3, entry 14). In most cases, the isolated yields for the pure products without further purification were greater than 90%.

In summary, we have developed a rapid and convenient synthesis of acylsulfonamides directly from commercially available polymer-supported reagents and scavengers. In addition, this mild reaction procedure is highly amenable for automation and can be easily adapted to parallel synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.158.

References and notes

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5. SiliCycle. http://www.silicycle.com.
6. The desired amount of DMAP was dissolved in 1 ml of CH_2Cl_2 and transferred via pipet to a pre-packed cartridge of Si-SCX (1 g, 0.8 mmol/g). The filtrate was collected via gravity filtration. The cartridge was washed with additional amounts of CH_2Cl_2 (MeOH for Table 2, entry 3). The filtrate was analyzed by LC/MS. No peak was detected for Table 2, entries 1–4. When 0.8 mmol DMAP was used (Table 2, entry 5), the filtrate was dried down and weighed, 15% of DMAP was recovered after the flow-through.
7. *General procedure:* To a 20 ml scintillation vial was added 0.3 mmol of PS-DCC (1.5 equiv, 1.2 mmol/g) followed by 0.2 mmol acid and 0.2 mmol sulfonamide in 2 ml of CH_2Cl_2. DMAP (0.2 mmol) is added to the above solution and the reaction mixture was shaken at room temperature on a J-Chem heater/shaker. The reaction was checked periodically by LC/MS. In most cases, the reaction was completed within 1 h. The reaction mixture was directly transferred via a pipet to a pre-packed cartridge of 1 g Si-SCX (0.8 mmol loading) via gravity filtration. The cartridge was washed with additional amounts of CH_2Cl_2 until no peak was detected in the fractions collected. The filtrate was combined and dried down. In all cases but one (Table 3, entry 9), the products thus collected have greater than 97% purity as determined by NMR and LC/MS without the need for any further purification. Products from entry 9 was purified by reverse-phase HPLC. When there is basic functionality in the product (entry 14), the crude material was purified by reverse-phase HPLC without filtering through a Si-SCX cartridge.