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Solid Phase Synthesis of Substituted Aminosulfonyl Ureas Using a Sulfonylcarbamate Linker

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Abstract: A procedure for preparing substituted aminosulfonyl ureas on solid support is described. Chemoselective reaction of chlorosulfonyl isocyanate with the Wang resin followed by reaction with an amine provides resin-bound substituted aminosulfonylcarbamates. Heating of the resultant resin in THF with a second amine provides the desired substituted aminosulfonyl ureas in good yield and purity.
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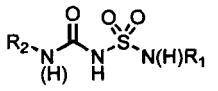
The use of solid supports for the generation of small organic molecules is rapidly becoming a key component of the drug discovery process. There has been interest recently in the development of new linker and release strategies that are essentially traceless and as such, provide terminal groups on cleavage different from the carboxylic acids or amides from much of the early peptide work.[1] In addition some of these strategies allow for the introduction of another diversity element concurrent with the cleavage off of the resin.[2] There have been many recent reports concerning new linkers such as the silicon linkers for phenyl groups as described by Ellman[3] and a carbamate linker for the preparation of sulfonamides described by Raju.[4] As part of our effort to develop synthetic strategies for the preparation of diverse libraries for high throughput screening, we have developed methodology for the preparation of substituted aminosulfonylureas **1** on solid support.



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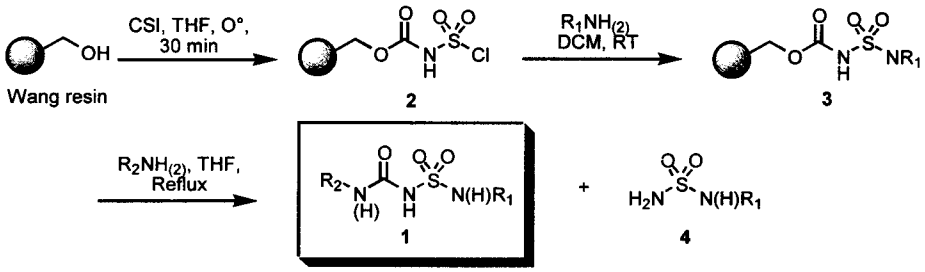
Aminosulfonylureas have been reported to have activity as hypoglycaemic agents,[5] ACAT inhibitors[6] and herbicides.[7] These compounds contain an acidic proton on the nitrogen atom between the sulfonyl and carbonyl groups that in solution can form base addition salts which can be alkylated. Solution phase synthesis[6] has been performed by the stepwise addition of nucleophiles to chlorosulfonyl isocyanate, (CSI), a highly reactive bis-electrophile.[8] We believed that a similar strategy would prove useful provided the initial reaction of CSI with Wang resin (CH_2OH) would be selective, and that after reaction of the chlorosulfonylcarbamate with an amine, the resultant substituted aminosulfonylcarbamate would be amenable to nucleophilic attack at the carbamate carbonyl. We report on a method for the solid phase synthesis of substituted aminosulfonylureas.

Our synthetic route, which is shown in Scheme 1, begins with the reaction of CSI with Wang resin in THF at 0° C to provide the chlorosulfonylcarbamate, **2**. Conversion to the substituted amino sulfonylcarbamate **3** is accomplished by reaction with excess amine ($R_1NH_{(2)}$) in DCM at room temperature. Treatment of **3** with an amine ($R_2NH_{(2)}$) in THF at reflux overnight, provided the substituted aminosulfonyl urea **1**. We wished to investigate the range of amines that would be tolerated at R_1 and whether the R_2 amines could be used as a limiting reagent so that the scope could extend beyond the narrow range of relatively volatile amines. It was our intent to avoid chromatography or the use of scavenger resins to remove the non-volatile amines used in excess.[9]

Scheme 1



Four different resin-bound substituted aminosulfonylcarbamates were prepared and reacted with amines as the limiting reagent in order to evaluate the generality of the method (Table 1).[10] Our results indicate that secondary amines in R_1 provide better overall yields and significantly higher purity than primary amines. Use of aniline (entries v- bb) as the first amine provided little or none of the desired products. During the synthesis of the library an impurity that was constant within a family of substituted aminosulfonylcarbamates, yet independent of the amine ($R_2NH_{(2)}$), was detected. The structure of the impurity was determined by NMR and mass spectroscopy to be the sulfamamide, **4**. Because this impurity was much more substantial when a limiting amount of nucleophile was employed, a competing solvolysis reaction was occurring.[11] In general, there was a correlation between nucleophilic strength and the amount of sulfamamide (**4**) produced, with stronger nucleophiles reacting at rate faster than the solvolytic cleavage reaction. In addition, we believe that the electronic character of the sulfonamide amine also may play a subtle role in this competing reaction.

Table 1

Entry	Amine $R_1NH_{(2)}$	Amine $R_2NH_{(2)}$	% Yield*	% Purity**
a	1-[4,4'bis((4-F)Ph)butyl}piperazine	$HN(CH_2)_5$	89	66
b	"	H_2NPh	83	50
c	"	H_2NCH_2Ph	quant.	77
d	"	$H_2N(CH_2)_2CH(CH_3)_2$	96	50
e	"	$H_2NPh(4\text{-}OMe)$	quant.	46
f	"	1-[4,4'bis((4-F)Ph)butyl}piperazine	59	80
g	"	$H_2NPh(4\text{-}F)$	26	58
h	$PhCH_2NH(CH_2)_2Ph$	$HN(CH_2)_5$	34	51
i	"	H_2NPh	95	54
j	"	H_2NCH_2Ph	65	87
k	"	$H_2N(CH_2)_2CH(CH_3)_2$	quant.	63
l	"	$H_2NPh(4\text{-}OMe)$	87	54
m	"	1-[4,4'bis((4-F)Ph)butyl}piperazine	58	40
n	"	$H_2NPh(4\text{-}F)$	quant.	51
o	H_2NCH_2Ph	$HN(CH_2)_5$	quant.	31
p	"	H_2NPh	79	64
q	"	H_2NCH_2Ph	80	47
r	"	$H_2N(CH_2)_2CH(CH_3)_2$	93	16
s	"	$H_2NPh(4\text{-}OMe)$	77	62
t	"	1-[4,4'bis((4-F)Ph)butyl}piperazine	50	13
u	"	$H_2NPh(4\text{-}F)$	quant.	62
v	H_2NPh	$HN(CH_2)_5$	55	38
w	"	H_2NPh	65	12
x	"	H_2NCH_2Ph	65	36
y	"	$H_2N(CH_2)_2CH(CH_3)_2$	83	19
z	"	$H_2NPh(4\text{-}OMe)$	70	0
aa	"	1-[4,4'bis((4-F)Ph)butyl}piperazine	40	27
bb	"	$H_2NPh(4\text{-}F)$	98	36

*Yield refers to the amount of recovered material. **Crude purity of desired product after cleavage from the resin determined by reverse phase HPLC at 220 nm. In cases where the purity is less than 50%, the major identifiable impurity is the sulfamamide, 4.

In conclusion, we have developed a method for the solid phase preparation of substituted aminosulfonyl ureas, and explored the scope and limitations thereof. Preparation of a resin-bound substituted aminosulfonylcarbamate followed by reaction with amines having strong nucleophilic character provided substituted aminosulfonyl ureas in good yield and purity. Since there are large numbers of cyclic and acyclic secondary amines available, coupled with the even larger number of amines with appropriate nucleophilic strength, an almost limitless number of structurally diverse compounds can be synthesised.

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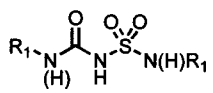
10. Wang resin (2.0 g, 1.08 mmole) was swelled in THF (50 ml) placed under N_2 and cooled to 0° C with agitation. Chlorosulfonyl isocyanate (5.4 mmole) was added over 10 minutes. The reaction was agitated for 30 minutes at 0° C. The resin was filtered under a N_2 blanket, washed with 5 portions of THF, 5 portions of DCM, transferred to a flask and swelled in DCM, 150 ml. An amine (10.8 mmole) was added and the reaction was agitated overnight at room temperature. The resin was filtered, washed with 3 portions DMF, 3 portions MeOH, 3 portions DCM/HOAc (9:1), and 6 portions DCM and dried in vacuo. To the resultant resin (0.042 mmole) swelled in anhydrous THF was added the second amine (0.031 mmole) and the mixture was heated at 66° C overnight. The resin was filtered, washed with THF and DCM and the combined filtrates evaporated. HPLC analysis was performed on YMC J'sphere H80 ™, 5 cm., 3:7 CH_3CN/H_20, 0.1% TFA to 9:1 CH_3CN/H_2O, 0.1 % TFA, over 5 minutes. Mass spectra were obtained with ES^-. NMR spectra were obtained at 300 and 600 MHz. on selected compounds after purification by semi-preparative HPLC. Data for entry **h**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.1 (m, 10H); 4.58 (s, 2H); 3.54 (t, J = 8.5 Hz, 2H); 3.30 (s, 4H); 2.75 (t, J = 8.5 MHz, 2H); 1.58 (s, 6H). MS(ES^-) 400 (M-H). MS(AP^+) 402 (M+H).
11. All four substituted amino sulfonylcarbamates in the absence of nucleophile were heated in THF at 66° C overnight. In most cases a nearly quantitative yield of the corresponding sulfamamide (**4**) was observed. In cases where the yield was less than quantitative a second major impurity was separated by semi-preparative HPLC. These impurities were identified by NMR and MS(ES^-) to be the corresponding products formed by the addition of second equivalent of the R_1 amine (product **5**). This result is undoubtedly the consequence of incomplete removal of the $R_1NH_{(2)}$ amine during the washing steps.



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