Solid Phase Synthesis of N-Alkyl Sulfonamides

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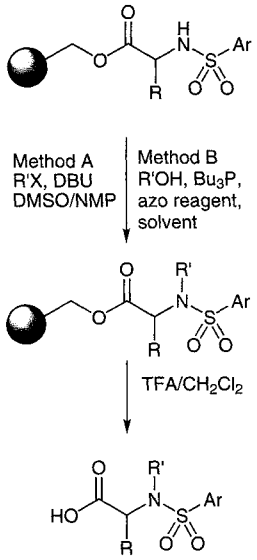
Abstract: Polymer-supported sulfonamides were alkylated using alkyl halides in the presence of DBU or with alcohols via the Mitsunobu reaction.

Solid phase synthesis has recently gained popularity as a result of its relative ease of automation and the emergence of high-throughput screening. This has been confirmed by the plethora of publications recently in this area of chemistry.[1] In this paper, we describe our results involving the alkylation of polymer supported sulfonamides[2] using either a direct alkylation[3] with various alkyl halides and DBU (method A) or the Mitsunobu[4] protocol (method B). The general reaction scheme is illustrated below.



Alkylations using method A were studied first and the results are shown in Table 1. The alkylation of sulfonamides with primary alkyl bromides or benzylic chlorides in general gave pure products (entries 1-24 see Table 1). Bromides susceptible to β-elimination (entries 28-29), sterically hindered bromides (entry 25),[5] or compounds containing a β-bromoamide functionality (entries 26-27)[6] did not give satisfactory yields. These alkylations were performed on PS-SASRIN which were commercially available as the Fmoc-protected amino acids. The Fmoc group was removed using 20% piperidine in DMF. The sulfonamide was attached using 3 eq. $ArSO_2Cl$ and 3 eq. Et_3N in CH_2Cl_2 overnight (Ar = 4-$MeOC_6H_4$). The desired alkylation was accomplished using 6 eq. of the alkyl halide, 6 eq. of DBU in 1:1 DMSO/NMP overnight. All the reactions were carried out in test tubes with magnetic stirring. The N-methylations were also demonstrated to work on the Advanced ChemTech ACT 357 with the caveat that the alkylations were performed twice to obtain >80% conversion to the desired alkylated sulfonamide. The products were analyzed by HPLC and the identities of all products were confirmed by MS. The N-methylated alanine compound (entry 8, Table 1) was further characterized by ^1H NMR, and gravimetric analysis indicates a 98% isolated yield.

The alkylation of sulfonamides under Mitsunobu conditions has been reported in solution phase using 1,1'-(azodicarbonyl)dipiperidine (ADDP) or 1,1'-azobis(N,N-dimethylformamide) (TMAD) with tributylphosphine (Bu_3P) in benzene.[8] The Mitsunobu reaction has been shown to work well on solid-phase for the preparation of ethers,[9] phosphonate esters,[10] carboxylic acid esters,[11] thioesters,[12] but has not previously been used to prepare N-alkyl sulfonamides on solid support. We chose to develop the Mitsunobu alkylation of sulfonamides on solid-phase to prepare compounds that we were unable to synthesize cleanly by Method A. Moreover, there are also a larger number of commercially available alcohols than alkyl bromides that could provide a more diverse set of alkylated products.

In order to optimize the conditions for Mitsunobu alkylation we utilized the Argonaut Nautilus 2400. Initial studies investigated changes in resin (PS-Wang-Gly and ArgoGel-Wang-Gly), solvent (toluene or methylene chloride) and azo reagent (ADDP or TMAD). The results are summarized in Table 2. From this study it was concluded that ArgoGel was the most effective resin based on purity. Moreover, the reaction could be run equally well in CH_2Cl_2 or toluene with either azo reagent without compromising product purity.

Table 1 - Alkylations of resin bound sulfonamides using Method A

Entry	Amino acid derivative	R'X	Percent purity[7]
1	Val	MeI	84%
2	Tyr	MeI	87%
3	Lys	MeI	95%
4	Glu	MeI	89%
5	Ser	MeI	95%
6	Thr	MeI	97%
7	Met	MeI	92%
8	Ala	MeI	99%
9	Phe	MeI	99%
10	Gly	MeI	96%
11	Ile	MeI	88%
12	Leu	MeI	97%
13	Gly	BnBr	93%
14	Gly	$BnOCOCH_2Br$	85%
15	Gly	$PhCOCH_2Br$	92%
16	Gly	$cHexCH_2Br$	73% + 22% SM
17	Gly	$cHexCH_2CH_2Br$	94%
18	Gly	$PhCO_2CH_2CH_2Br$	97%
19	Gly	$PhthNH(CH_2)_4Br$	96%
20	Gly	$4\text{-}BrPhNHCOCH_2Br$	81%
21	Gly	$PhOCH_2CH_2Br$	96%
22	Gly	$2,6\text{-}Cl_2BnBr$	98%
23	Gly	4-ClBnCl	94%
24	Gly	$4\text{-}MeOPh(CH_2)_3Br$	98%
25	Gly	$PhSO_2CH_2Br$	all SM
26	Gly	$PhCONHCH_2CH_2Br$	all SM
27	Gly	$PhthNHCH_2CH_2Br$	34% + 65% SM
28	Gly	$4\text{-}BrPhNHCO(CH_2)_2Br$	all SM
29	Gly	$PhCH_2CH_2Br$	24% + 67% SM

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Table 2 - Optimization of Solid Phase Mitsunobu Reaction

	Resin	Azo reagent	Solvent system	R'OH	Percent purity[7]
1	PS-Wang	ADDP	toluene	4-PhPhCH$_2$OH	88%
2	PS-Wang	ADDP	toluene	Ph(CH$_2$)$_3$OH	77%
3	PS-Wang	ADDP	CH_2Cl_2	4-PhPhCH$_2$OH	93%
4	PS-Wang	ADDP	CH_2Cl_2	Ph(CH$_2$)$_3$OH	77%
5	PS-Wang	TMAD	toluene	4-PhPhCH$_2$OH	87%
6	PS-Wang	TMAD	toluene	Ph(CH$_2$)$_3$OH	66%
7	PS-Wang	TMAD	CH_2Cl_2	4-PhPhCH$_2$OH	94%
8	PS-Wang	TMAD	CH_2Cl_2	Ph(CH$_2$)$_3$OH	70%
9	ArgoGel-Wang	ADDP	toluene	4-PhPhCH$_2$OH	100%
10	ArgoGel-Wang	ADDP	toluene	Ph(CH$_2$)$_3$OH	92%
11	ArgoGel-Wang	ADDP	CH_2Cl_2	4-PhPhCH$_2$OH	97%
12	ArgoGel-Wang	ADDP	CH_2Cl_2	Ph(CH$_2$)$_3$OH	74%
13	ArgoGel-Wang	TMAD	toluene	4-PhPhCH$_2$OH	100%
14	ArgoGel-Wang	TMAD	toluene	Ph(CH$_2$)$_3$OH	87%
15	ArgoGel-Wang	TMAD	CH_2Cl_2	4-PhPhCH$_2$OH	100%
16	ArgoGel-Wang	TMAD	CH_2Cl_2	Ph(CH$_2$)$_3$OH	83%

With these results in hand, an array of alkylated sulfonamides were prepared using the Argonaut Nautilus 2400. ADDP was selected as the azo reagent due to its reduced cost and toluene as a solvent due to slight improvements in purity observed in the optimization study (Table 2). A library of compounds was prepared using two different resins, two different amino acids, four different alcohols and two different sulfonyl chlorides to provide 16 different products, whose results are illustrated in Table 3.

The reactions illustrated in Tables 2 and 3 were performed by adding 6 eq of Bu_3P (1 M in the indicated solvent system) to the resin followed by 6 eq of the alcohol (1 M in THF). The reactions were cooled to -10°C and 6 eq azo reagent (1 M in CH_2Cl_2) was added. The reactions were warmed to room temperature and agitated for 12 hrs. After a washing regimen, the products were cleaved from the resin with 50% TFA/CH_2Cl_2. HPLC and MS were performed on all products to determine purity and composition. In addition a ^{1}H NMR was obtained on compound #4, in Table 3 and gravimetric analysis indicated a 100% yield.

From these results shown in Table 3 we can conclude that α-substituted amino acid derived substrates work equally well as glycine in the Mitsunobu alkylations. It is apparent that sterically hindered alcohols like cyclohexylmethanol are not good substrates for Mitsunobu alkylations, but proceed nearly to completion using Method A. Phenethyl alcohol in this case works well as opposed to the alkylation with the corresponding bromide. In conclusion, we have demonstrated that a large number of different types of sulfonamides can be prepared on solid phase by alkylation or Mitsunobu reaction. Optimization of reaction conditions for the Mitsunobu alkylation has been facilitated by automated methods.

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Table 3 - Library of 16 sulfonamides prepared on Argonaut Nautilus 2400

	Resin	Amino acid	ArSO$_2$Cl	R'OH	Percent purity[7]
1	ArgoGel-Wang	Gly	pMeOPhSO$_2$Cl	cHexCH$_2$OH	31%
2	ArgoGel-Wang	Gly	pMeOPhSO$_2$Cl	BnOH	88%
3	ArgoGel-Wang	Gly	pMeOPhSO$_2$Cl	PhCH$_2$CH$_2$OH	76%
4	ArgoGel-Wang	Gly	pMeOPhSO$_2$Cl	Ph(CH$_2$)$_3$OH	80%
5	ArgoGel-Wang	Gly	TsCl	cHexCH$_2$OH	48%
6	ArgoGel-Wang	Gly	TsCl	BnOH	89%
7	ArgoGel-Wang	Gly	TsCl	PhCH$_2$CH$_2$OH	82%
8	ArgoGel-Wang	Gly	TsCl	Ph(CH$_2$)$_3$OH	81%
9	ArgoGel-Wang	Phe	pMeOPhSO$_2$Cl	cHexCH$_2$OH	31%
10	ArgoGel-Wang	Phe	pMeOPhSO$_2$Cl	BnOH	92%
11	ArgoGel-Wang	Phe	pMeOPhSO$_2$Cl	PhCH$_2$CH$_2$OH	88%
12	ArgoGel-Wang	Phe	pMeOPhSO$_2$Cl	Ph(CH$_2$)$_3$OH	80%
13	ArgoGel-Wang	Phe	TsCl	cHexCH$_2$OH	35%
14	ArgoGel-Wang	Phe	TsCl	BnOH	96%
15	ArgoGel-Wang	Phe	TsCl	PhCH$_2$CH$_2$OH	88%
16	ArgoGel-Wang	Phe	TsCl	Ph(CH$_2$)$_3$OH	90%
17	PS-Wang	Gly	pMeOPhSO$_2$Cl	cHexCH$_2$OH	33%
18	PS-Wang	Gly	pMeOPhSO$_2$Cl	BnOH	81%
19	PS-Wang	Gly	pMeOPhSO$_2$Cl	PhCH$_2$CH$_2$OH	73%
20	PS-Wang	Gly	pMeOPhSO$_2$Cl	Ph(CH$_2$)$_3$OH	73%
21	PS-SASRIN	Phe	pMeOPhSO$_2$Cl	cHexCH$_2$OH	26%
22	PS-SASRIN	Phe	pMeOPhSO$_2$Cl	BnOH	96%
23	PS-SASRIN	Phe	pMeOPhSO$_2$Cl	PhCH$_2$CH$_2$OH	88%
24	PS-SASRIN	Phe	pMeOPhSO$_2$Cl	Ph(CH$_2$)$_3$OH	73%

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