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Michael addition of amines to vinyl sulfonamides on solid support

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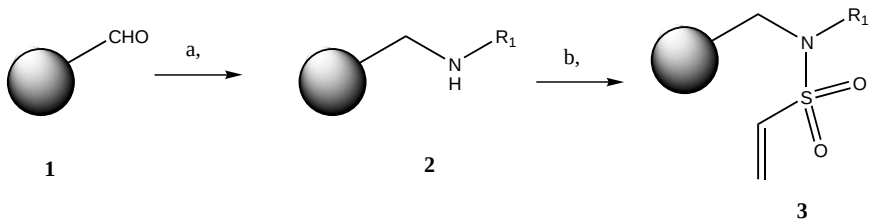
Abstract—A solid phase synthesis for Michael addition of amines to vinylsulfonamides has been developed. The method enables synthesis of β-aminosulfonamides with high yields and purity. Further functionalization of adducts derived from primary amines is demonstrated.

Michael adducts of vinylamides and vinylsulfonamides play an essential role in drug discovery. A large number of entries in the CMC and MDDR databases contain the β-amino amide or sulfonamide moiety.[1] In addition, β-amino sulfones are important for several physiological processes.[2] Synthesis of β-amino ketones, esters or sulfones via Michael addition has been described under mild conditions.[3] Such Michael additions can often be effected by amines with or without catalyst at room temperature. Acryloyl Wang and vinylsulfonylmethyl resins have also been described and are commercially available as supports for the synthesis of tertiary amines. Loading is usually achieved by conjugate addition of primary or secondary amines at room temperature, while the tertiary amine products are released by β-elimination of the quaternary amine under basic conditions. However, similar reactions of amines with vinylsulfonamide Michael acceptors have been less cited. In solution, a β-dimethylaminoethylsulfonamide derivative has been synthesized with an ethanolic solution of excess dimethylamine as part of a structure–activity study for the α_2-adrenoreceptor.[4] The vinylsulfonamide moiety can be readily prepared in solution by tandem sulfonylation–elimination when 2-chloroethylsulfonylchloride is reacted with amines in the presence of base. However, to date no synthesis of β-aminoethylsulfonamides has been reported on solid support.

En route to the vinylsulfonamide intermediate, the formyl functionalized acid sensitive resin **1** was subjected to reductive amination with an amine building block using the previously described method[5] to prepare secondary amine **2**. Analogous to the known solution phase procedure, resin **2** was treated with 2-chloroethylsulfonylchloride and excess DIEA in dichloromethane to yield vinylsulfonamide **3** (Scheme 1). A small amount of the resin was cleaved with TFA to verify that the desired product was obtained in high yield and purity. The above resin was used for our attempts to effect Michael addition on solid support with or without catalyst. We decided to investigate the efficiency of two Lewis acids to accelerate the reaction. $Yb(OTf)_3$ has widely been used to accelerate epoxide opening in solution,[6] while $LiClO_4$ has been the preferred reagent



1 **2** **3**

Scheme 1. Synthesis of vinylsulfonamides. (a) 1% AcOH in DMF/R_1NH_2/$NaBH(OAc)_3$; (b) $ClCH_2CH_2SO_2Cl$/DIEA/DCM.

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for similar reactions on the solid phase.[7] A reactive piperazine building block (**4a**–**e**, Table 1) was selected to find the optimal conditions for the conjugate addition (Scheme 2). No reaction was observed with large excess of amine without the presence of Lewis acids (**4a**), as expected. Test reactions in solution phase showed a similar pattern; no conjugate addition occurred with one to fivefold excess of the amine without the presence of Lewis acids (data not shown). The concentration of $Yb(OTf)_3$ could not be increased beyond 6 mg/mL either in THF or in a mixture of dichloromethane and 2-propanol due to poor solubility. $LiClO_4$, however, was soluble in large excess and gave rise to significantly higher conversion (**4b**) than $Yb(OTf)_3$ at room temperature (**4c**). In addition, a mixture of dichloromethane and 2-propanol (**4d**) was found to be superior to THF with respect to product yield. In both solvents, the only products obtained were the desired Michael adduct and starting material. Finally, full conversion to β-aminoethylsulfonamides was achieved at elevated temperatures in high purity (**4e**). Michael adducts derived from primary amines were amendable to subsequent acylation with acyl chlorides to yield to corresponding amides (**6a**–**b**). Other electrophiles, which are beyond the scope of this report, can be reacted with similar success.

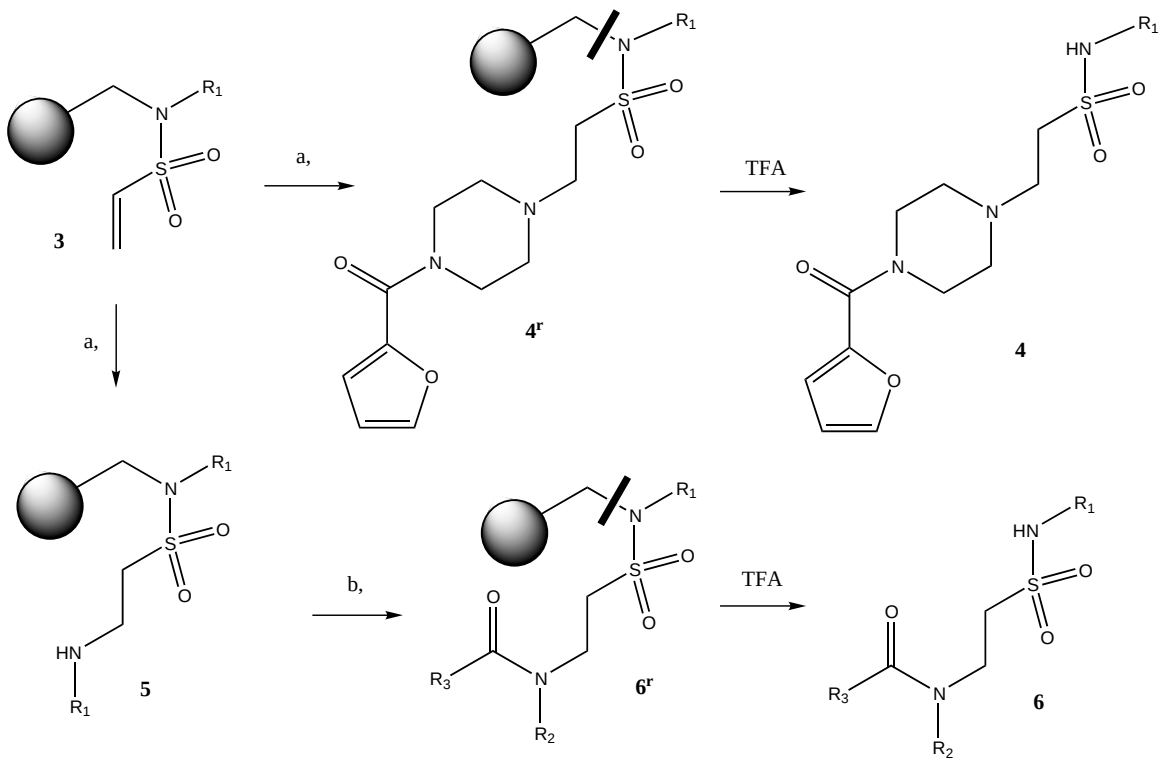
In summary, a facile synthesis of β-aminoethylsulfonamides and β-amidoethylsulfonamides has been demonstrated. The optimal procedure involves excess $LiClO_4$ and amine building blocks at elevated temperatures. Our methodology enables the synthesis of combinatorial libraries in parallel or with the split-and-pool technique.[8]

Experimental details. 4-(4-Formyl-3-methoxyphenoxy)-butyryl AM resin was purchased from Novabiochem. Lithium perchlorate must be handled with utmost care because it is a strong oxidizer and it may ignite or explode on contact with combustible materials. ^1H NMR spectra were recorded with a Brucker 300 NMR spectrometer. Typical procedure for the synthesis

Table 1. Synthesis of Michael adducts. R_1, *p*-methylbenzylamine

	Amine (R_1)	R_2	Solvent	*T* (°C)	Lewis acid	Purity	MS
4a	4-Furoylpiperazine	–	DCM:IPA	25	None	0	–
4b	4-Furoylpiperazine	–	THF	25	$LiClO_4$	5	392
4c	4-Furoylpiperazine	–	DCM:IPA	25	$Yb(OTf)_3$	0	–
4d	4-Furoylpiperazine	–	DCM:IPA	25	$LiClO_4$	50	392
4e	4-Furoylpiperazine	–	DCM:IPA	75	$LiClO_4$	99	392
6a	4-MeO-benzylamine	2,5-DiMeOPhCH_2COCl	DCM:IPA	75	$LiClO_4$	99	527
6b	4-F-Phenethylamine	*o*-Toluoyl chloride	DCM:IPA	75	$LiClO_4$	99	469

Purity is by HPLC–ELSD. Impurity was starting material in all cases. MS values are for M+H ions.



Scheme 2. Synthesis of aminoethylsulfonamides. (a) Amine/$LiClO_4$/DCM/IPA; (b) R_3COCl/DIEA/DCM.

of Michael adducts. Resin **2** (0.05 mmol) in dichloromethane (2 mL) was treated with DIEA (176 μL, 1.0 mmol) followed by 2-chloroethylsulfonyl chloride (44 μL, 0.5 mmol). The mixture was shaken for 2 h at rt. The resin was filtered and washed with DCM, IPA, DCM (3× each) and dried to yield resin **3**. To resin **3** (0.025 mmol) in a pyrex tube was added $LiClO_4$ (53 mg, 0.5 mmol), dichloromethane (1 mL) and 2-propanol (1 mL). Amine (0.5 mmol) was then added and the tube was tightly capped. The mixture was shaken at 75°C for 24 h. The resin was filtered and washed with DCM, IPA and DCM (3× each). This step was repeated one more time (double coupling) to yield resins **4** and **5**. To resin **5** (0.025 mmol) was added dichloromethane (1 mL), DIEA (44 μL, 0.25 mmol) followed by acid chloride (0.125 mmol) and the mixture was shaken for 5 h at room temperature. The resin was filtered and washed with DCM, IPA, DCM (3× each) and dried. All products[9] were cleaved off the resin with a cocktail of TFA:H_2O (95:5, 1 mL) for 1 h.

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9. Typical ^{1}H NMR spectra for products follow. **4e**: (^{1}H NMR, 300 MHz, acetone-d_6): δ 7.73 (s, 1H), 7.29 (d, 2H), 7.17 (d, 2H), 7.06 (s, 1H), 6.61 (s, 1H), 4.70 (s, 2H), 4.10 (bs, 4H), 3.64 (m, 2H), 3.38 (m, 4H), 2.30 (s, 3H). **6a**: (two rotamers, ^{1}H NMR, 300 MHz, acetone-d_6): δ 7.30–7.10 (m, 6H), 6.95–6.73 (m, 6H), 4.63–4.53 (s, 2H), 4.20 (d, 2H), 3.85–3.60 (m, 13H), 3.25–3.15 (m, 2H), 2.32 (d, 3H). **6b**: (two rotamers, ^{1}H NMR, 300 MHz, acetone-d_6): δ 7.45–6.95 (m, 12H), 4.32 (s, 2H), 3.93 (m, 2H), 3.42 and 3.12 (2×t, 4H), 3.00 and 2.78 (2×t, 2H), 2.31 (s, 3H), 2.21 (s, 3H).