A Convenient Synthesis of *N*-Alkyl-(*E*)-1-alkenesulfonamides

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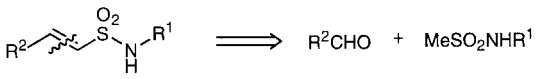
Abstract: A series of vinylsulfonamides **3** has been synthesised through a condensation of *N*-Boc-methanesulfonamides **1** and aldehydes **2**. *O*-Boc-2-hydroxyalkanesulfonamides were identified as intermediates, arising from N–O transfer of the Boc group. Elimination of OBoc gave the vinylsulfonamides.

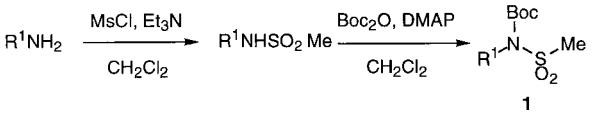
The sulfonamide group has found wide usage in medicinal chemistry as a metabolically stable polar group. 1-Alkenesulfonamides (vinylsulfonamides), however, have received relatively little attention. A noteworthy example of their use in bioorganic chemistry and a pointer to their potential is Gennari's "vinylogous sulfonamidopeptides."[1] Sulfonamides have classically been prepared by the reaction of sulfonyl chlorides and amines. As part of a broad medicinal chemistry programme, targeted towards the synthesis of sulfonamides, an alternative disconnection strategy was sought. In order to avoid the synthesis of sulfonyl chlorides, which frequently requires harsh conditions, and to provide ready access to *N*-substituted vinylsulfonamides, the introduction of the sulfonamide as a prefabricated unit was considered. To this end, the illustrated disconnection was explored (Figure).



Figure

Realisation of this strategy has been achieved on few occasions. Aldehydes have been used in the Peterson reaction of α-silylsulfonamides[2] and the Wittig–Horner reaction of *N,N*-dimethyl(diethoxy)methylsulfonamide.[3] Both approaches were limited to *N,N*-dimethylsulfonamides and the former suffered variable stereoselectivity. Styrenesulfonamides have also been prepared by a Knoevenagel-type condensation[4] and the base mediated reaction of α-halosulfonamides with benzyl halides.[5] Thompson has reported the *C*-alkylation of *N*-alkanesulfonamide dianions with a variety of electrophiles.[6] The utility of this approach has been duly recognised in the subsequent literature,[7] in particular the reaction with aldehydes to produce 2-hydroxyalkanesulfonamides.[8] In the case of two arylaldehydes Thompson reported the conversion of the 2-hydroxyalkanesulfonamides to the corresponding styrenesulfonamides by mesylation and base induced elimination.[6] We would like to report herein a complementary method that achieves vinylsulfonamide synthesis in a single step through the condensation of aldehydes and methanesulfonamides.

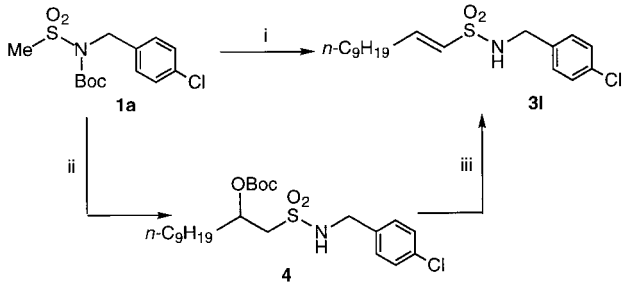
Having experienced somewhat variable returns from Thompson's two step dianion route, we investigated the possibility of *N*-protection using the *t*-butoxycarbonyl (Boc) group. The *N*-Boc-methanesulfonamides **1** of a variety of alkylamines were readily prepared, in high yields, from the corresponding methanesulfonamides by reaction with di-*t*-butyl dicarbonate in the presence of catalytic 4-dimethylaminopyridine (DMAP) (Scheme 1).



Scheme 1

For its ease of preparation, the derivative of 4-chlorobenzylamine, **1a**, was used for much of the initial work and the results of its reaction with a series of aldehydes are set out in the Table (entries 1–14). The anion of **1a** was generated at -78°C with one equivalent of potassium *t*-butoxide (*t*-BuOK) and allowed to react with arylaldehydes **2a-i** to give vinylsulfonamides **3a-i**, respectively, in good yields and excellent *trans*-stereoselectivity. The reaction was not sensitive to the nature and position of the aryl substituents of the aldehydes.

None of the anticipated 2-hydroxyalkanesulfonamides were observed and the absence of the Boc group was marked. However, when the reaction was attempted with decylaldehyde **2l** a mixture (3:1) of the vinylsulfonamide **3l** and the *O*-Boc-2-hydroxyalkanesulfonamide **4** (Scheme 2) was obtained. From analysis of the reaction by thin layer chromatography it appeared that **4** was formed initially and during the course of the reaction underwent elimination to give **3l**.[9] It seemed, therefore, that the condensation of the aldehyde and sulfonamide fragments was followed by a rapid intramolecular N–O transfer of the Boc group.

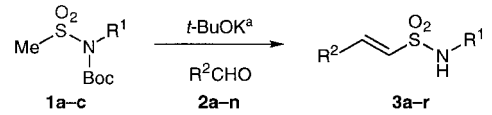


Scheme 2. i) *t*-BuOK (2eq.), -78°C, 1h, then *n*-C_9H_{19}CHO (**2l**), -78–20°C, 18h (67%). ii) *t*-BuOK (1eq.), -78°C, 1h, then *n*-C_9H_{19}CHO (**2l**), -78–20°C, 1h (74%). iii) Cs_2CO_3, anhydrous MeOH (87%)

It was found that products **3l** and **4** could be prepared selectively by varying the reaction conditions: the use of a second equivalent of *t*-BuOK facilitated vinylsulfonamide synthesis, with an efficiency comparable to that of the arylaldehydes (Table, entry 12);[10] and the reaction was halted at the intermediate product **4** by reducing the reaction time (Scheme 2).[11] The intermediacy of **4** was further suggested through its ready conversion to **3l** under basic conditions, with cesium carbonate in anhydrous methanol being of particular practical value (Scheme 2).

Using two equivalents of *t*-BuOK, several other non-arylaldehydes underwent the single step conversion to vinylsulfonamides (Table, entries 10–14). Increasing steric bulk of the aldehyde did not have a deleterious effect as judged by cyclohexylcarboxaldehyde **2m** and pivaldehyde **2n** (entries 13 and 14). It is worth noting that potentially

Table. The Synthesis of Vinylsulfonamides



1a–c **2a–n** **3a–r**

Entry	R^1	1	R^2	2	3	Yield (%)[b]
1	4-$ClC_6H_4CH_2$	**1a**	C_6H_5	**2a**	**3a**	56
2	4-$ClC_6H_4CH_2$	**1a**	4-ClC_6H_4	**2b**	**3b**	87
3	4-$ClC_6H_4CH_2$	**1a**	2-FC_6H_4	**2c**	**3c**	96
4	4-$ClC_6H_4CH_2$	**1a**	3-FC_6H_4	**2d**	**3d**	87
5	4-$ClC_6H_4CH_2$	**1a**	4-FC_6H_4	**2e**	**3e**	86
6	4-$ClC_6H_4CH_2$	**1a**	2-$NO_2C_6H_4$	**2f**	**3f**	71
7	4-$ClC_6H_4CH_2$	**1a**	3-$NO_2C_6H_4$	**2g**	**3g**	86
8	4-$ClC_6H_4CH_2$	**1a**	4-$NO_2C_6H_4$	**2h**	**3h**	69
9	4-$ClC_6H_4CH_2$	**1a**	2-Furyl	**2i**	**3i**	76
10	4-$ClC_6H_4CH_2$	**1a**	CH_2=CH	**2j**	**3j**	67
11	4-$ClC_6H_4CH_2$	**1a**	(*E*)-PhCH=CH	**2k**	**3k**	78
12	4-$ClC_6H_4CH_2$	**1a**	*n*-C_9H_{19}	**2l**	**3l**	67
13	4-$ClC_6H_4CH_2$	**1a**	C_6H_{11}	**2m**	**3m**	80
14	4-$ClC_6H_4CH_2$	**1a**	*t*-Bu	**2n**	**3n**	60
15	*n*-Bu	**1b**	4-ClC_6H_4	**2b**	**3o**	81
16	*n*-Bu	**1b**	*n*-C_9H_{19}	**2l**	**3p**[c]	68
17	C_6H_{11}	**1c**	4-ClC_6H_4	**2b**	**3q**	76
18	C_6H_{11}	**1c**	*n*-C_9H_{19}	**2l**	**3r**	80

[a] For entries 10–14, 16 and 18 two equivalents of *t*-BuOK were used; one equivalent was used in all other instances. [b] Isolated yields after column chromatography. All new compounds gave satisfactory elemental analyses and ^{1}H NMR data. [c] A mixture of double bond stereoisomers *E*/*Z* = 9:1

useful[12] 1,3-butadiene-1-sulfonamides **3j** and **3k** were easily prepared from acrolein **2j** and *trans*-cinnamaldehyde **2k**, respectively (entries 10 and 11).

The reaction was not limited to benzylamine derivatives. It was applied successfully to the *n*-butylamine compound **1b** (entries 15 and 16) and the cyclohexylamine compound **1c** (entries 17 and 18) for both alkyl- and arylaldehydes. The reaction in the majority of cases showed a high selectivity for the *trans*-double bond. A small amount of a (*Z*)-vinylsulfonamide was observed for the least sterically demanding combination of substrates, the two straight chain alkyl components **1b** and **2l**.

The choice of *t*-BuOK followed an extensive study of alternative bases, from which it was concluded that this base was much to be preferred for the one-pot reaction. Lithium diisopropylamide can be used in its place for the synthesis of intermediate **4** and compounds of its like. As an indication of the scope and limitations of this approach, it is worth noting that the anion of **1a** was stable at -78°C, but at room temperature, in the absence of an electrophile, the methanesulfonyl group was eliminated to give *N*-Boc-4-chlorobenzylamine. In preliminary investigations, it was found that this was a competing pathway for less reactive electrophiles such as ketones.

In conclusion, the synthesis of vinylsulfonamides has been demonstrated for a range of aldehydes and *N*-Boc-methanesulfonamides. *O*-Boc-2-hydroxyalkanesulfonamides were shown to be intermediates that underwent elimination either *in situ* or as a separate reaction. Thus, the N–O transfer of the Boc group was identified as the key step *en route* to vinylsulfonamides. Reduction of the double bond of vinylsulfonamides has been demonstrated,[1a] so this route may be additionally provide access to alkanesulfonamides. The wider application of this approach will be reported in due course.

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between ethyl acetate (20ml) and saturated ammonium chloride (20ml). The aqueous phase was extracted twice with ethyl acetate (20ml). The combined organic phases were washed with water and brine and dried over magnesium sulfate. Filtration and evaporation of the filtrate afforded the crude product mixture, which was purified by column chromatography (silica; 65% dichloromethane/toluene). The vinylsulfonamide **3l** was isolated as a colourless solid (359mg, 67%). ^{1}H NMR (300MHz, $CDCl_3$): 7.32(2H, m); 7.26(2H, m); 6.77(1H, dt, *J* 15, 6.9Hz); 6.13(1H, dt, *J* 15, 1.5Hz); 4.49(1H, t, *J* 6.3Hz); 4.17(2H, d, *J* 6.9Hz); 2.21(1H, dt, *J* 6.9, 1.5Hz); 2.19(1H, dt, *J* 6.9, 1.5Hz); 1.43(2H, m); 1.28(12H, br s); 0.89(3H, t, *J* 6.8Hz). Anal. Calcd. for $C_{23}H_{38}ClNO_5S$: C 58.03, H 8.05, N 2.94%; Found: C 58.05, H 8.26, N 3.04%.

11. The procedure for the preparation of compound **4** was as for vinylsulfonamide **3l** with the following modifications: one equivalent of *t*-BuOK was used; the cold bath was removed as soon as the aldehyde had been added; and the mixture was stirred for 1h. ^{1}H NMR (300MHz, $CDCl_3$): 7.34(4H, m); 5.00(1H, m); 4.28(2H, d, *J* 6.3Hz); 3.28(1H, dd, *J* 14.9, 8.6Hz); 3.01(1H, dd, *J* 14.9, 3.1Hz); 1.65(1H, m); 1.54(1H, m); 1.48(9H, s); 1.27(14H, s); 0.89(3H, t, *J* 6.8Hz). Anal. Calcd. for $C_{18}H_{28}ClNO_2S$: C 60.40, H 7.89, N 3.91%; Found: C 60.64, H 7.74, N 3.91%.

12. For a perspective of the area: Lee, Y. S.; Ryu, E. K.; Yun, K.-Y.; Kim, Y. H. *Synlett* 1996, 247. **Table**. The Synthesis of Vinylsulfonamides.