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Conjugate addition of sodium methanesulfinate to vinyl pyridines and diazines for the synthesis of aliphatic sulfones

Gregory M. Schaaf *, Sabuj Mukherjee, Alex G. Waterson

GlaxoSmithKline, Oncology Research & Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA

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ABSTRACT

A convenient method to introduce a sulfone group to pyridines and diazines is described. This efficient method involves the conjugate addition of sodium methanesulfinate to vinyl heterocycles. This process tolerates a wide variety of functional groups and is performed in the presence of acetic or trifluoroacetic acid. A one-pot, two-step synthesis of sulfones starting from the corresponding heteroaryl halide is also described.

Sulfone-containing molecules are prevalent throughout medicinal chemistry. The sulfone moiety has the ability to affect many physicochemical properties as a consequence of its electron-withdrawing character.[1] It has found use in its ability to attenuate the basicity of amines as well as affect the pK_a of hydrogen bond donors. The dipolar aprotic nature of the sulfone makes it a hydrogen bond acceptor while its non-charged nature may help increase cellular penetration.[2] The sulfone group is isoelectronic to a phosphate[2] and is an isostere to a carbonyl. Sulfones are the terminal oxidation state for sulfides and sulfoxides and thus may have reduced metabolic liabilities.[3]

Aryl sulfones can be found in many marketed drugs, such as the triptan Relpax® used to treat migraines.[4] There are also several prominent examples of aliphatic sulfones, such as the nitrogen-linked ethyl methyl sulfone in the kinase inhibitor Tykerb®, which is indicated for ErbB2 (HER2) positive breast cancer.[5] A carbon-linked ethyl methyl sulfone may be another way to introduce this important functionality to drug-like molecules (Fig. 1).

Carbon-linked sulfones are synthesized by several methods (Scheme 1). Synthesis of alkyl halide **2** followed by displacement with sodium methanesulfinate[8] or sodium methyl sulfide followed by oxidation[6] provides the desired product. A similar reaction sequence beginning with halomethylketones can also be used,[7] adding an additional reduction step.

Additionally, aryl sulfinic acids have been shown to participate in 1,4-addition reactions. These sulfinic acids (**3**), prepared from the corresponding chlorosulfinates, react with acrylic acid to form propanoic acids **4**.[9] A wide variety of other Michael acceptors have been explored as well.

As part of a medicinal chemistry effort to synthesize kinase inhibitors containing small aliphatic side chains, we wanted to incorporate an alkyl sulfone into molecules of interest. It was thought that sodium methanesulfinate could be nucleophilic enough to undergo conjugate addition to heterocyclic vinyl substrates, specifically vinyl pyridines and diazines, to provide aliphatic sulfones (**5**). These vinyl substrates can be easily synthesized from the corresponding halide by a variety of methods. This two-step sequence would be a substantial improvement over traditional methods described above.

Initial development focused on 2-vinyl pyridine as the substrate for conjugate addition (Table 1). The use of five equivalents of

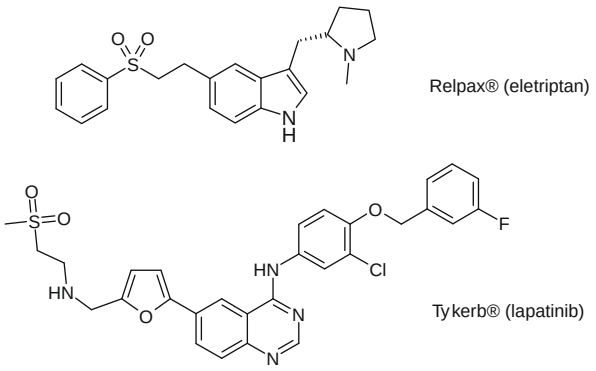

Figure 1. Marketed drugs containing sulfones.

* Corresponding author. Tel.: +1 919 357 2991.
E-mail address: gms4b@hotmail.com (G.M. Schaaf).

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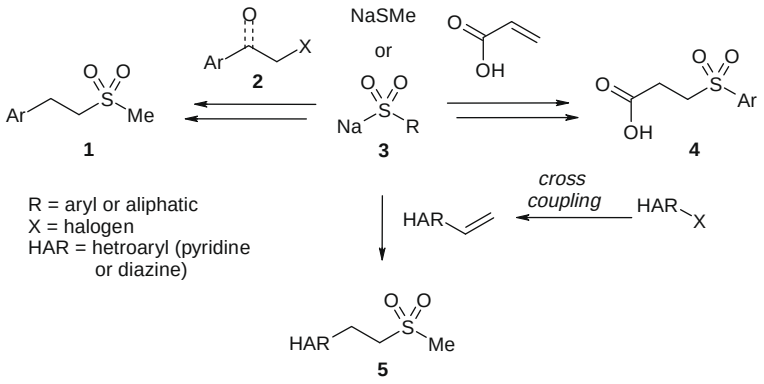
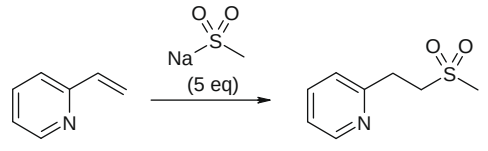


Scheme 1. Strategies for sulfone synthesis.

Table 1
Reaction of 2-vinyl pyridine with sodium methanesulfinate



Entry	Acids	Eq. acid	Time (h)	Temp (°C)	Solvent	Yield (%)
1	HOAc	100	2	60	EtOH	88
2	HOAc	5	2.5	60	EtOH	88
3	HOAc	1	20	60	EtOH	91
4	HOAc	0.5	24	60	EtOH	45
5	HOAc	10	6	rt	EtOH	79
6	HOAc	5	24	60	Toluene	57
7	HOAc	5	24	55	THF	29
8	HOAc	5	24	35	DCM	85
9	H_3BO_4	10	24	60	EtOH	85
10	HCl	5	8	60	EtOH	85
11	TFA	5	0.5	60	EtOH	89
12	TFA	1	4	rt	EtOH	85
13	$BF_3{\cdot}Et_2O$	2	24	−78 to rt	DCM	77

sodium methanesulfinate was standard throughout the experiments.[10] In entry 1, a large excess of acetic acid in ethanol[11] (~1:1 HOAc/EtOH) affects this conversion at 60 °C in only 2 h. Decreasing the amount of HOAc to 5 equiv (entry 2) had little effect on the outcome of the reaction, providing the sulfone product in excellent yield in 2.5 h. The reaction time is extended to 20 h if only 1 equiv of acetic acid is used. This reaction can also be carried out at room temperature (entry 5) but requires extended reaction times and additional acid. Exposure to substoichiometric amounts of HOAc resulted in incomplete conversion (entry 4) and recovered starting material. In the absence of acid no reaction occurred (data not shown).

Several additional solvents were explored using 5 equiv of HOAc. Toluene as a solvent (entry 6) provided the product in modest yield. Low conversion was observed with tetrahydrofuran as the solvent. However, dichloromethane (entry 8) proved to be an attractive aprotic alternative to EtOH, providing **7** in 85% yield, albeit with an extended reaction time.

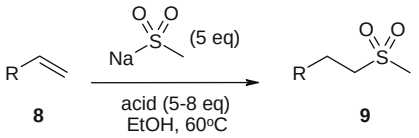
We explored additional acids. Exposure of the reactants to H_3BO_4 (entry 9) in EtOH at reflux provided **7** in excellent yield but with higher loading (10 equiv). Hydrochloric acid (entry 10) worked well, though it required longer reaction time compared to HOAc. Gratifyingly, trifluoroacetic acid (TFA) substantially increased the efficiency and versatility of the process, especially compared to HOAc. Substituting 5 equiv of TFA for the acid provided the sulfone in only 30 minutes in refluxing EtOH. Reducing the equivalents of TFA to one and decreasing the temperature to room temperature still provided the product in excellent yield in only 4 h (entry 12). Several Lewis acids, including $FeCl_3$, $AlCl_3$, and $TiCl_4$, were surveyed with DCM as the solvent. Using $BF_3{\cdot}Et_2O$ (entry 13) provided the most promising results and suggests that Lewis acids could be used as an alternative to protic acids.

Next, we included pyridines and diazines of various substitution patterns (Table 2). Substrates containing an assortment of functional groups were included. Acetic acid and TFA were chosen since they offer complementary profiles. Flexibility in the equivalents and strengths of these acids balanced with the choice of temperature and time offer a range of conditions to satisfy substrate compatibility.

The basicity of the nitrogen of the heterocycle must be taken into consideration. Only substrates with a pK_a greater than ~5 should be significantly protonated by HOAc and participate in the reaction. These substrates generally include pyridine and other electron-rich pyridines. Trifluoroacetic acid is strong enough to protonate less basic substrates, such as pyridines with electron-withdrawing groups and most substituted diazines. Additionally, an appreciable amount of TFA is likely consumed neutralizing sodium methanesulfinate to form methanesulfinic acid. Thus, for less basic substrates it is necessary to add TFA (8 equiv) in excess of the amount of sodium methanesulfinate (5 equiv) to assure free acid in the reaction mixture.

While several of the vinyl pyridines are commercially available, most substrates were synthesized from the corresponding halide and Molander's vinyltrifluoroborate.[12] The location of the vinyl group on the substrate is critical. Exposure of the 4-vinyl pyridine to acetic acid and sodium methanesulfinate (entry 1) provided the product in excellent yield. As expected, 3-vinyl pyridines, even basic ones such as **8b**, failed to render any product. Consequently, differentiation between two vinyl groups is possible. Prepared from the 2,3-dibromopyridine, divinyl pyridine **8c** reacts only at the vinyl group on the 2-position to provide **9c** exclusively. In the presence of TFA, a wide range of electron-poor and electron-rich vinyl pyridines are converted to the ethyl methyl sulfone (entries 4–7) with less basic nitropyridine **8g** requiring TFA for conversion. Interestingly, the Boc group of aminopyridine **8h** remains intact under TFA conditions to cleanly provide the sulfone. Pyridyls **8i** and **8j** which contain substituted vinyl groups achieved only moderate success. Both 2-vinyl quinoline and quinoxaline (entries 11 and 12) failed to undergo conversion using acetic acid, but were converted in high yield in the presence of TFA. Interestingly, 2-vinylpyrazine **8m** was converted to the sulfone in the presence of HOAc even though it is only weakly basic.[13] The reaction proceeded in excellent yield for a variety of 2-vinyl pyrimidines (entries 14–16), including the scaffold for a kinase inhibitor (**8q**).[14]

Table 2
Reaction of substituted vinyl pyridines and diazines with sodium methanesulfinate



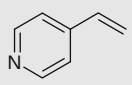
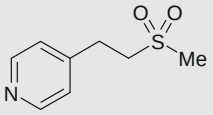
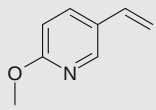
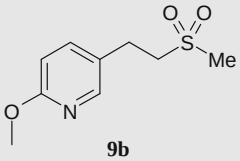
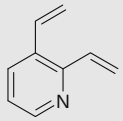
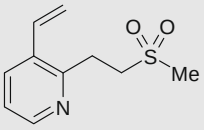
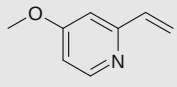
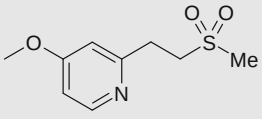
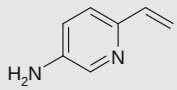
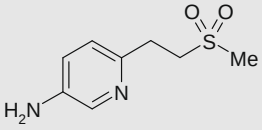
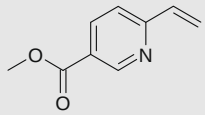
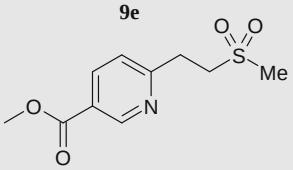
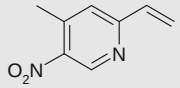
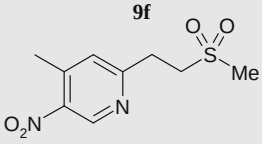
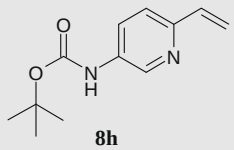
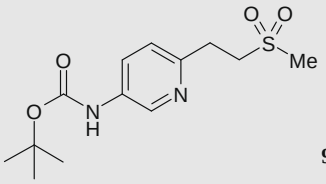
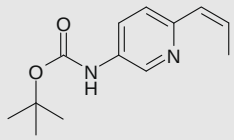
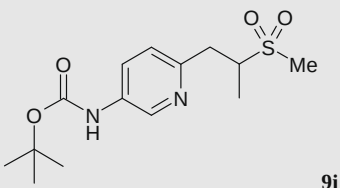
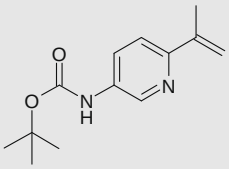
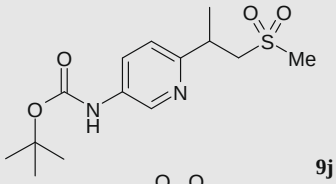
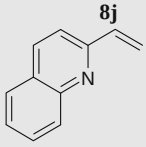
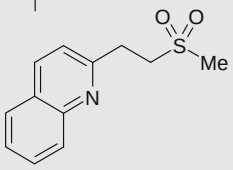
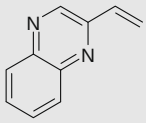
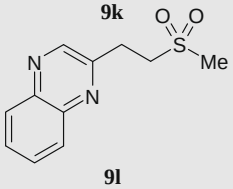
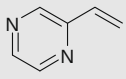
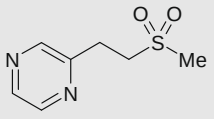
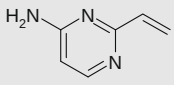
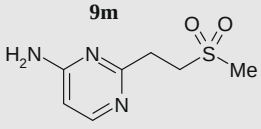
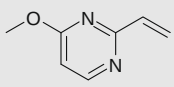
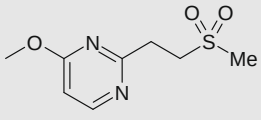
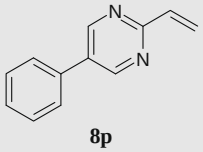
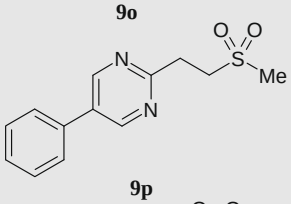
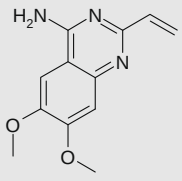
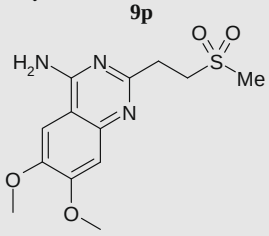
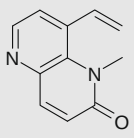
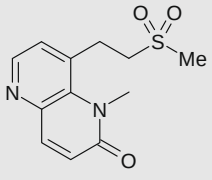
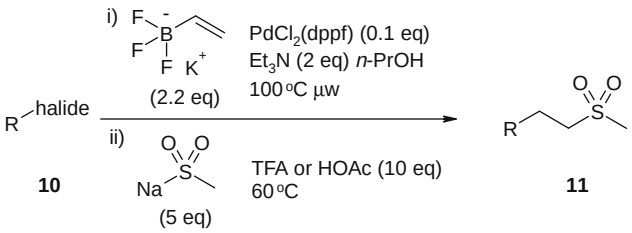
Entry	Vinyl **8**	Sulfone **9**	pK_a[a]	Acid	Time[b] (h)	Yield[c] (%)
1	 **8a**	 **9a**	5.0	HOAc	6	91
2	 **8b**	 **9b**	6.3	TFA HOAc	20 20	NR NR
3	 **8c**	 **9c**	4.6	TFA HOAc	4 6	79 83
4	 **8d**	 **9d**	6.3	TFA	4	78
5	 **8e**	 **9e**	8.7	TFA	20	62
6	 **8f**	 **9f**	2.9	TFA	2	86
7	 **8g**	 **9g**	1.6	TFA HOAc	6 20	65 NR
8	 **8h**	 **9h**	4.6	TFA HOAc	2 20	94 NR
9	 **8i**	 **9i**	4.8	TFA	20	50

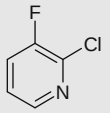
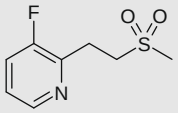
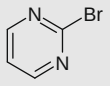
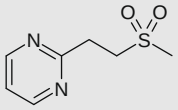
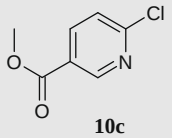
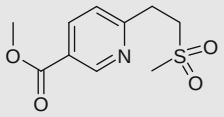
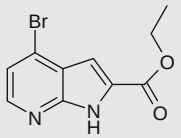
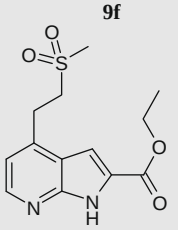
Table 2. (*continued*)

Entry	Vinyl **8**	Sulfone **9**	pK_a[a]	Acid	Time[b] (h)	Yield[c] (%)
10	 **8j**	 **9j**	4.8	TFA	20	37
11	 **8k**	 **9k**	4.9	TFA HOAc	20 20	88 NR
12	 **8l**	 **9l**	0.7	TFA HOAc	6 20	91 NR
13	 **8m**	 **9m**	0.7	HOAc	5	79
14	 **8n**	 **9n**	5.4	TFA	6	51
15[d]	 **8o**	 **9o**	2.5	TFA	6	81
16	 **8p**	 **9p**	0.7	TFA	2	87
17	 **8q**	 **9q**	6.2	TFA	2	70
18[e]	 **8r**	 **9r**	1.0	TFA	2	62

[a] ACD labs.
[b] If incomplete after 20 h, the reaction was quenched and isolated. Typically, unreacted starting material was recovered.
[c] Avg isolated yields of two runs.
[d] Use of 2,2,2-trifluoroethanol prevents displacement of the OMe group.
[e] 2 equiv of sodium methanesulfinate.

Table 3
One-pot conversion of substituted heteroaryl halides to sulfones



Entry	Halide **10**	Sulfone **11**	Time (h)	Yield (%)
1[a]	 **10a**	 **11a**	8	71
2[a]	 **10b**	 **11b**	2	62
3[a]	 **10c**	 **9f**	2	66
4[b]	 **10d**	 **11d**	2	68

[a] TFA was used.
[b] HOAc was used.

Due to low MW and volatility, there were several substrates which we could not easily prepare or isolate, such as 3-fluoro-2-vinyl pyridine. Since both the coupling and addition reactions take place in similar alcoholic solvents (EtOH and *n*-PrOH), we considered a one-pot method[15] where the vinyl compound is not isolated following the Suzuki reaction. This simplified procedure eliminates the isolation of volatile vinyl intermediates for low MW substrates as well as providing a convenient procedure for complex heteroaryl chlorides (Table 3).

Accordingly, we subjected fluoropyridine **10a** to the usual Suzuki conditions. Upon completion, the vinyl intermediate was directly treated with sodium methanesulfinate and acid[16] to provide sulfone **11a** in excellent yield. Another low MW compound, pyrimidine **10b**, was also converted to the corresponding sulfone in good yield. For ester **10c**, the yield of the one-pot sequence (66%) compares favorably to the combined yields of the sequential two-step process (72%), and eliminates purification of the vinyl intermediate. This transformation also worked well for azaindole **10d**, a common scaffold for many medicinal chemistry efforts.[14]

We have found that a wide variety of vinyl pyrimidines and diazines undergo conjugate addition with sodium methanesulfinate under acidic conditions to provide the corresponding ethyl methyl sulfones. The basicity of the nitrogen, indicated by its pK_a, can guide the choice of a strong or weak acid. Additionally, a one-pot method directly converts halo pyrimidines and diazines to sulfones, eliminating the need to isolate vinyl intermediates. This convenient procedure allows for the rapid generation of sulfone-containing compounds.

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References and notes

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10. (a) With 3 equiv of sodium methanesulfinate, the reaction time was extended to 20 h for the same conditions as shown in entry 2 of Table 1. With 1.5 equiv, the reaction time was extended to 36 h. (b) *Representative procedure*: To a mixture of methyl 6-ethenyl-3-pyridinecarboxylate (80 mg, 0.49 mmol, 1.0 equiv) and sodium methanesulfinate (250 mg, 2.45 mmol, 5.0 equiv) in EtOH (3.0 mL, 0.16 M) was added TFA (0.18 mL, 2.45 mmol, 5.0 equiv). The mixture was heated at 60 °C for 2 h. The reaction mixture was quenched with $NaHCO_3$ (aq) and extracted twice with DCM. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 100 mg (84%) of sulfone **9f** as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.00 (d, J = 1.83 Hz, 1H), 8.22 (dd, J = 8.15, 2.29 Hz, 1H), 7.54 (d, J = 8.06 Hz, 1H), 3.86 (s, 3H), 3.52–3.62 (m, 2H), 3.21–3.29 (m, 2H), 3.00 (s, 3 H).
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13. This may represent a limitation in the software (ACD labs) used to calculate the pK_a's or incomplete knowledge of the system.
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15. *Representative one-pot procedure*: To a stirring mixture of ethyl 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (150 mg, 0.557 mmol, 1.0 equiv), potassium vinyl trifluoroborate (164 mg, 1.226 mmol, 2.2 equiv), and TEA (0.16 mL, 1.1 mmol, 2.0 equiv) in *n*-PrOH (5.6 mL, 0.1 M) was added $PdCl_2$(dppf) (41 mg, 0.056 mmol, 0.1 equiv). This reaction mixture was heated under microwave conditions (optional) for 30 min at 100 °C. The reaction mixture was transferred to a flask (for convenience) and treated with sodium methanesulfinate (285 mg, 2.79 mmol, 5.0 equiv) and HOAc (0.32 mL, 5.57 mmol, 10 equiv) and stirred at 60 °C for 2 h. The reaction mixture was concentrated to dryness, taken up in DCM, and absorbed onto silica. The product on silica was subjected to column chromatography using 10% 2 M NH_3 in MeOH/90% DCM solution and DCM as the solvents. Alternatively, NH_4OH in MeOH may be substituted for 2 M NH_3 in MeOH. In some instances it was necessary to perform an aqueous extraction of the product after column chromatography to remove TEA salts.
16. Ten equivalents of TFA or HOAc was added due to the additional 2 equiv of TEA used during the Suzuki reaction.