Exploration of One-Pot, Tandem Sulfamoylation and *Aza*-Michael Cyclization Reactions for the Syntheses of Oxathiazinane Heterocycles

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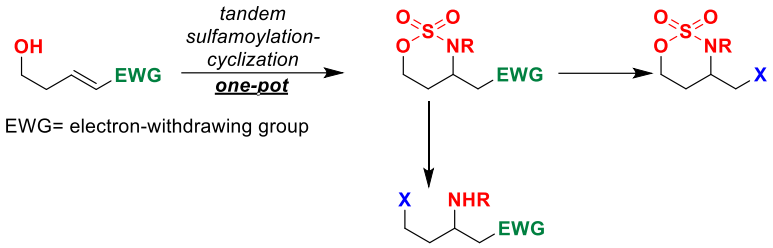
Supporting Information Placeholder

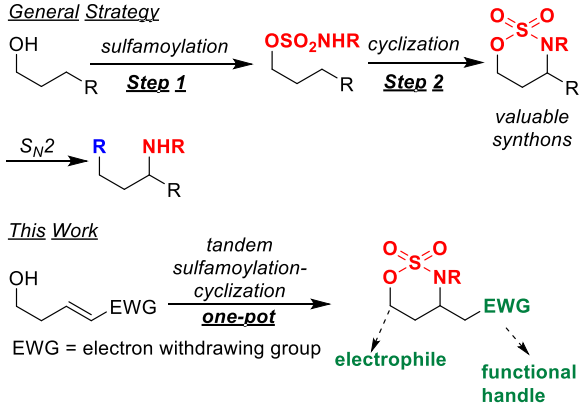


ABSTRACT: We show the first examples of one-pot, tandem sulfamoylation/*aza*-Michael reactions for the preparation of oxathiazinane heterocycles from linear alkenyl alcohol precursors. Our optimized protocols are tolerant of a variety of functional groups and provide products which are amenable for further transformations. The reactions scale well, and no special precautions are required to exclude air or ambient moisture.

Oxathiazinanes are now established synthetic intermediates for a variety of valuable targets.[1-4] The most common protocols to synthesize oxathiazinane heterocycles involve two-step, two-pot sequences (**Scheme 1**). Traditionally, a linear alcohol is converted into its corresponding sulfamate ester by base-promoted condensation with a sulfamoyl chloride.[5] Milder methods have also been developed which allow for the sulfamoylation of functional-group rich, sensitive substrates.[6-11] The resulting sulfamates are then cyclized using a variety of creative methods, which include C–H amination,[12, 13] *aza*-Wacker,[14-18] *aza*-Michael,[19] and strain-release reactions.[20, 21] In sharp contrast, we have found almost no examples of one-pot syntheses of oxathiazinanes from linear alcohol starting materials. Our laboratory has a programmatic focus on elevating the synthetic potential of the sulfamate functional group.[1] Here, we show the first examples of one-pot, tandem sulfamoylation/*aza*-Michael reaction cascades for the convenient preparation of oxathiazinane heterocycles from linear alkenyl alcohol substrates.

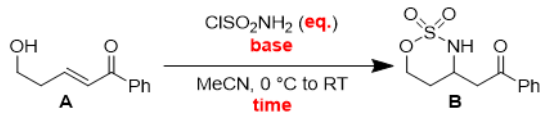
We chose (*E*)-5-hydroxy-1-phenylpent-2-en-1-one as a convenient test-substrate to optimize a potential one-pot sulfamoylation/*aza*-Michael reaction sequence. With ~2 equiv. of $ClSO_2NH_2$ (freshly prepared by the reaction of HCO_2H with $ClSO_2NCO$) and 2 equiv. of DABCO, we were pleased to observe desired product in a 16% yield (**Table 1**, **Entry 1**). The yield of product did not improve by replacing DABCO with TBAF (**Table 1**, **Entry 2**). Using 1,1,3,3-tetramethylguanidine, triethylamine, or pyridine in place of TBAF (**Table 1**, **Entries 3–5**) was far better. With 3 equivalents of pyridine and 3 equivalents of $ClSO_2NH_2$, the yield of desired product improved to 70% (**Table 1**, **Entry 6**).

Scheme 1. Oxathiazinane heterocycles are valuable but generally require two-step, two-pot protocols to prepare. One-pot reactions for their syntheses are rare.



Further increasing the equivalents of pyridine and $ClSO_2NH_2$ did not lead to marked improvement (**Table 1**, **Entry 7**). Using a solvent mixture of DMA and MeCN also gave product in a respectable yield of 70% (**Table 1**, **Entry 8**). With these conditions, quenching the reaction with saturated, aqueous $NaHCO_3$ solution and stirring this mixture for at least 10 minutes was essential for product formation. In trial runs where this quench was eliminated, only trace product was observed, suggesting the important role of $NaHCO_3$ in promoting cyclization.

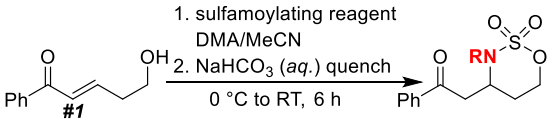
Table 1. Select Optimization Conditions.

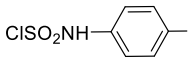
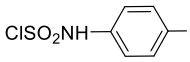
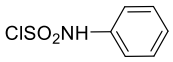


	Eq[a]	Base[b]	Time[c]	Yield of B
1	1.8	DABCO (2)	15 h	16%
2	1.8	TBAF (2)	15 h	10%
3	1.8	TMG[d] (2)	24 h	40%
4	2	NEt_3 (2)	6 h	43%
5	2	C_5H_5N (2)	15 h	48%
6	**3**	**C_5H_5N (3)**	**15 h**	**70%**
7	4	C_5H_5N (4)	15 h	77%
8	**2**	**DMA[e]**	**6 h**	**70%**

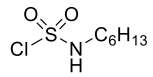
[a] Eq = equivalents
[b] equivalents in parentheses
[c] time shown in hours
[d] TMG = 1,1,3,3-tetramethylguanidine
[e] Ratio of DMA:MeCN = 1:2; $NaHCO_3$ (sat. aq.) quench is essential for product formation.

Scheme 2. Structure-Reactivity Relationship with Diverse Sulfamate Esters.

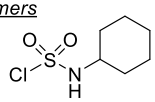


Entry	Sulfamoylating Reagent		Isolated Yield
1	$ClSO_2NCO/HCO_2H$	(**#2**)[a,b,c]	76% *[X-ray]*
2	$ClSO_2NHMe$	(**#3**)	76%
3	$ClSO_2NHEt$	(**#4**)	66%
4		(**#5**)	52%
5		(**#6**)	51%
6		(**#7**)	54%

Poor Performers



No Reaction

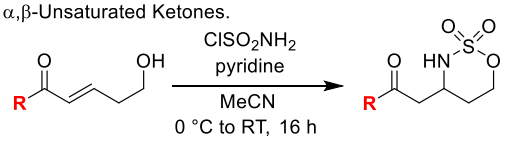


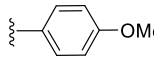
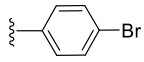
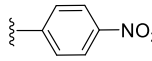
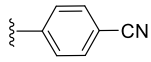
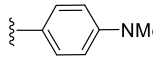
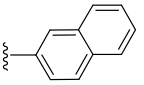
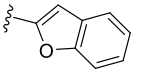
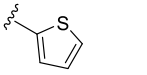
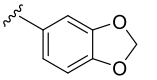
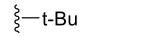
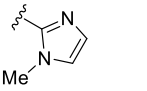
No Reaction

[a](product number)
[b] CCDC 2353012
[c]Please see supporting information for full experimental details including procedures and equivalents

We were able to confirm product identity by X-ray diffraction analysis (**Scheme 2**, **Entry 1**). We wondered if tandem sulfamoylation/*aza*-Michael reactions were possible with *N*-substituted sulfamoyl chlorides. We found that one-pot preparation of *N*-Me (**Scheme 2**, **Entry 2**), *N*-Et (**Scheme 2**, **Entry 3**), and *N*-aryl (**Scheme 2**, **Entries 4–6**) oxathiazinanes was possible. One-pot reactions failed with *N*-hexyl sulfamoyl chloride and *N*-cyclohexyl sulfamoyl chloride. Here, we hypothesize that the increased steric bulk of these alkyl substituents precluded *aza*-Michael cyclization. Aryl groups are also bulky, but the increased nucleophilicity of the aniline nitrogen compensated for this.

Scheme 3. Structure-Reactivity Relationship with Various α,β-Unsaturated Ketones.



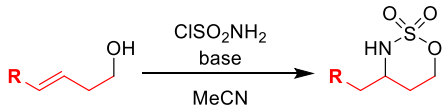
Entry	R (Michael Acceptor)		Isolated Yield[a]
1		(***#8, #9***)[b]	**69%**
2		(***#10, #11***)	**75%**
3		(***#12, #13***)	**71%**
4		(***#14, #15***)	**77%**
5		(***#16, #17***)	**17%**
6		(***#18, #19***)	**51%**
7		(***#20, #21***)	**66%**
8		(***#22, #23***)	**71%**
9		(***#24, #25***)	**61%**
10		(***#26, #27***)	**62%**
11		(***#28, #29***)	**78%**[c]

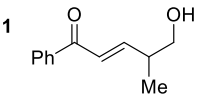
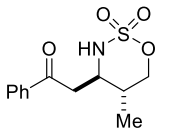
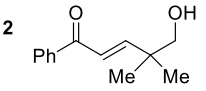
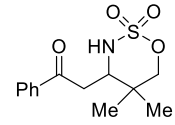
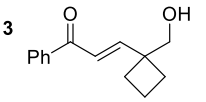
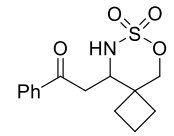
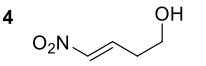
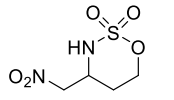
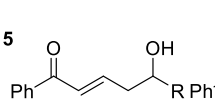
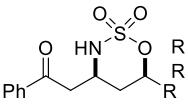
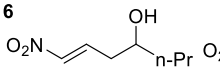
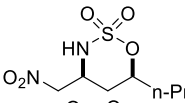
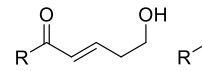
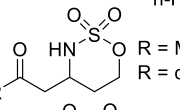
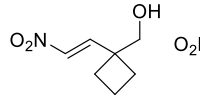
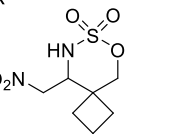
[a]Please see supporting information for full experimental details including procedures and equivalents.
[b](substrate number, product number)
[c]DMA was used in place of pyridine with a reaction time of 3 h.

Our optimized protocols were compatible with several α,β-unsaturated ketones (**Scheme 3** and **Scheme 4**). A variety of *para*-substituted aryl alkyl ketones reacted nicely (**Scheme 3**, **Entries 1 – 4**). We hypothesize that the strong electron donating ability of *p*-NMe_2 precluded efficient *aza*-Michael cyclization (**Scheme 3**, **Entry 5**). We were particularly pleased that several heteroarenes were compatible with our optimized conditions (**Scheme 3**, **Entries 7, 8,** and **11**). Dialkyl ketones also reacted well (**Scheme 3**, **Entry 10** and **Scheme 4**, **Entry 7**). In addition to α,β-unsaturated ketones, one-pot cyclization reactions with nitroalkenes were also possible (**Scheme 4**, **Entries 4**,**6**, and **8**). Where relevant, the cyclizations proceeded with synthetically useful diastereocontrol, and the reaction diastereoselectivities ranged from 3:1 to 5:1 (**Scheme 4**, **Entries 1**, **5**, and **6**). Oxathiazinanes with substituents in a 1,2-*anti*

configuration (**Scheme 4**, **Entry 1**) and a 1,3-*syn* configuration (**Scheme 4**, **Entries 5** and **6**) were favored. In each case, the major diastereomer has a lower energy chair conformation relative to the minor diastereomer, and it may be possible to use straightforward conformational analysis to predict product outcomes for substrates not depicted here.

Scheme 4. Examining Stereoselectivity and Functional Group Compatibility.

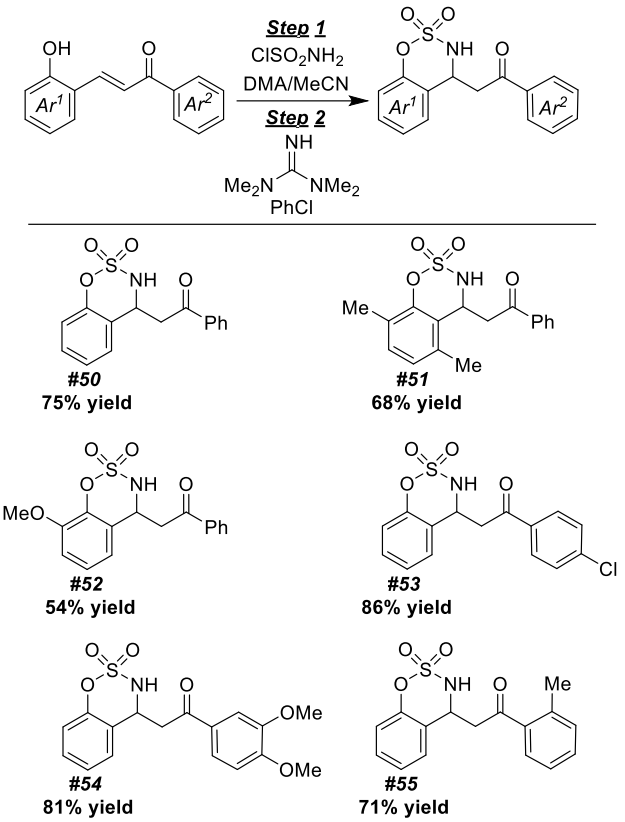


Entry	Substrate	Product		Isolated Yield[a]
1			(***#30***, ***#31***)[b]	48%[c] ***[X-ray]***
2			(***#32***, ***#33***)	58%
3			(***#34***, ***#35***)	60%
4			(***#36***, ***#37***)	60%
5			R = n-Pr (***#38***, ***#39***) R = Bn (***#40***, ***#41***)	60%[d] 56%[e]
6			(***#42***, ***#43***)	75%[f]
7			R = Me (***#44***, ***#45***) R = cy-hex (***#46***, ***#47***)	62% 65%
8			(***#48***, ***#49***)	77%

[a]Please see supporting information for full experimental details including procedures and equivalents.
[b](substrate number, product number)
[c]reaction dr = 3:1, major diastereomer depicted and confirmed by X-ray diffraction analysis (CCDC 2353013).
[d]reaction dr = 5:1, major diastereomer depicted and confirmed by nOe analysis.
[e]reaction dr = 3:1, major diastereomer depicted and confirmed by nOe analysis.
[f]reaction dr = 5:1, major diastereomer depicted and confirmed by nOe analysis.

While sulfamoylation of chalcones was very efficient, a one-pot *aza*-Michael cyclization did not occur in any substrate tested (**Scheme 5**). For these substrates, we found that treatment with 1,1,3,3-tetramethylguanidine in PhCl allowed for efficient cyclization, albeit in a second pot.

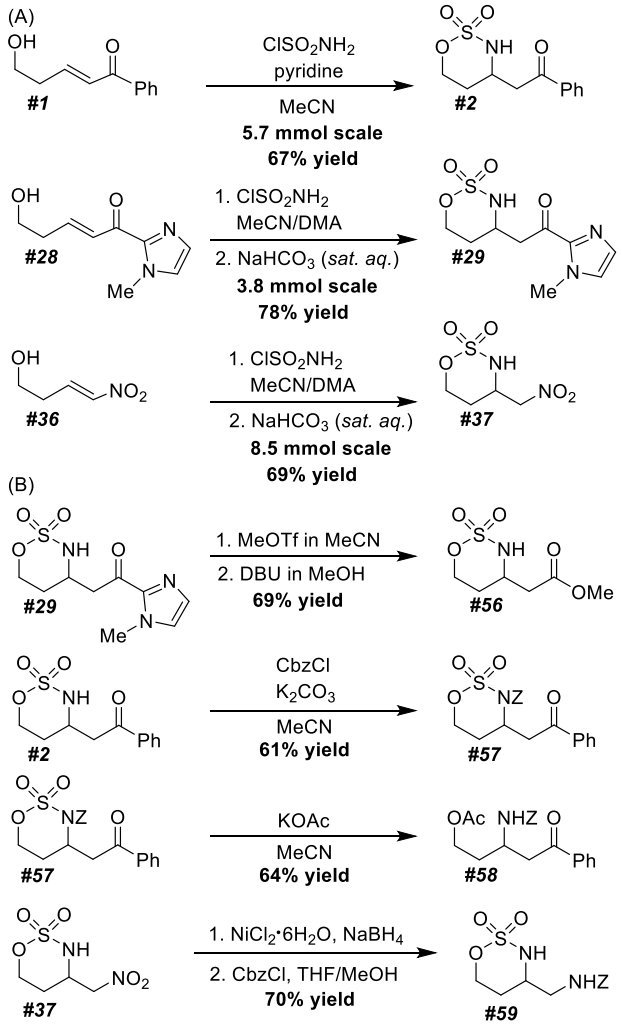
Scheme 5. Chalcone substrates require a two-pot protcol for efficient cyclizations.



Our optimized protocol was amenable to scaling up (**Scheme 6A**), and the products were convenient intermediates for further transformations (**Scheme 6B**). For example, the imidazole in **29** could be activated by methylation and then displaced with methanol to give ester **56**. The oxathiazinane ring of **2** could be activated by appending a Cbz group and then opened with KOAc to give protected amino-alcohol **58**. The nitro group of **37** could be reduced to a primary amine using a combination of $NiCl_2$•$6H_2O$ and $NaBH_4$ and then derivatized with CbzCl in one pot to give differentially protected diamine **59**.

In summary, we show the first examples of one-pot, tandem sulfamoylation/*aza*-Michael reactions for the preparation of oxathiazinane heterocycles from linear alkenyl alcohol precursors. Our optimized protocols are tolerant of a variety of functional groups and provide products which are amenable for further transformations. The reactions scale well, and no special precautions need be taken to exclude air or ambient moisture. We expect this technology to be a valuable addition to existing methods for preparing densely functionalized heterocycles.

Scheme 6. (A) Scale-up and (B) Applications.



ASSOCIATED CONTENT

Supporting Information

Supporting Information contains additional experimental details and NMR spectra.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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