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A general synthesis of quinolinones and benzothiazine 1,1-dioxides via ring closing metathesis

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Abstract

A general synthesis of quinolinones and benzothiazine 1,1-dioxides is presented. A series of *N*-phenylacrylamides and *N*-phenylethylenesulfonamides were studied for their ability to undergo ring closing methathesis to yield the corresponding quinolinones and benzothiazine 1,1-dioxides, respectively. The reactions are general in scope and represents a mild method for the preparation of these heterocycles.

Quinolinones are an interesting class of molecules present in a number of biologically active natural products. For example, this core is present in the antibiotics nybomycin and deoxynybomycin,[1] isolated from streptomycete cultures. This structural core is also employed in medicinal chemistry and is present in a number of medicinally valuable compounds. Figure 1 highlights several of these medicinally important compounds, and this figure also serves to illustrate the variety of substitution patterns incorporated in these molecules.[2a–d]

As part of our medicinal chemistry efforts, we had an occasion to incorporate a quinolinone structural motif in one of our target molecules. While several procedures have been reported for the synthesis of quinolinones,[3] they generally involve the use of strong bases and/or high temperatures thus limiting the functional group compatibility of these reactions. We envisioned that a ring closing metathesis (RCM) reaction of a suitable functionalized diene, such as **5** (Scheme 1), could represent a powerful method for the formation of this ring system. If successful, the functional group tolerability of this reaction would allow for a general entry into this class of heterocycles. In addition, we were also interested in exploiting this idea to prepare the corresponding cyclic sulfonamide system ($X = SO_2$ in Scheme 1). Sulfonamides[4] are an important functional group in medicinal chemistry, and these cyclic sulfonamides could potentially represent interesting bioisostere replacements for quinolinone ring systems. We wish to present in this Letter an attractive method for the preparation of quinolinones and benzothiazine dioxides via a RCM reaction.

Ring closing metathesis is widely used in synthetic organic chemistry and has become the method of choice for the formation of cyclic targets including heterocycles.[5] Several reports have appeared in the literature describing the use of RCM for the formation of lactams[6] and cyclic sulfonamides.[7] These studies clearly establish the utility of RCM for the synthesis of these ring systems. We envisioned that a RCM approach would be amenable toward the synthesis of quinolinones and benzothiazine 1,1-dioxides as outlined in Scheme 1. At the outset, the key question we wished to address regarding our strategy was whether *N*-phenylacrylamides and/or *N*-phenylethylenesulfonamides are viable substrates for RCM. Toward this goal, we elected to employ diene **7** as a model substrate

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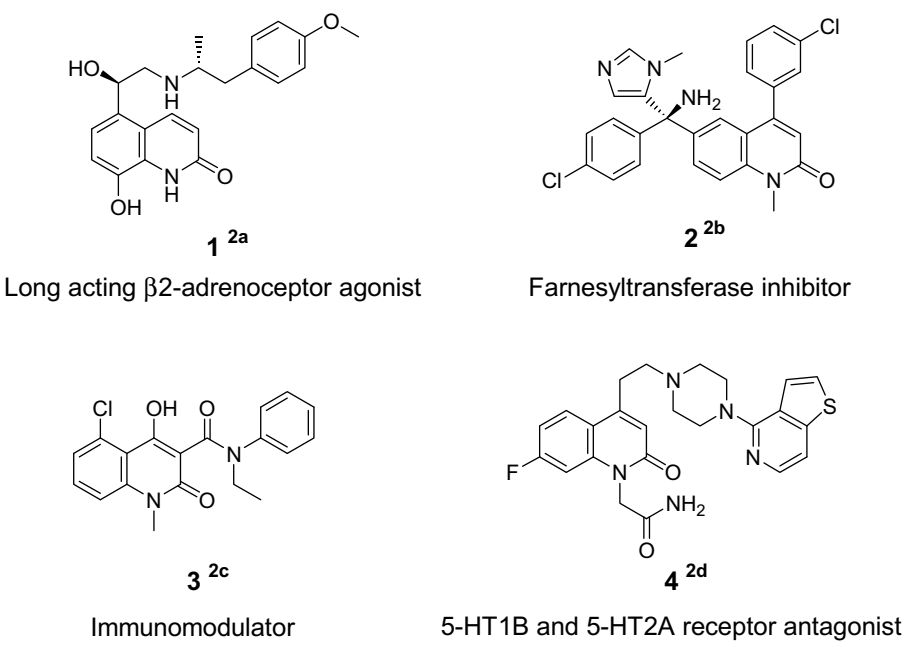
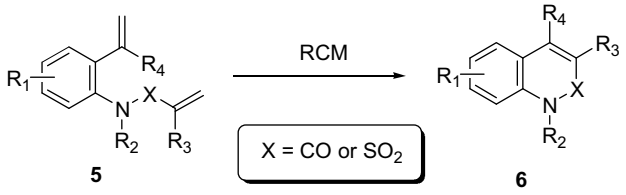


Fig. 1. Biologically active quinolinones.

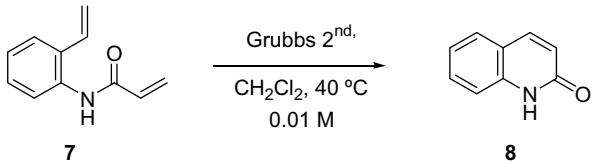


Scheme 1. RCM approach to quinolinones and benthothiazine 1,1-dioxides.

to investigate its reactivity in a RCM reaction. The results of these studies are summarized in Table 1.

Treatment of **7** with 10 mol % of Grubbs 2nd generation catalyst in dichloromethane cleanly yielded the desired quinolinone in 95% isolated yield. The catalyst loading could be reduced to either 5% or 2% without erosion in the efficiency of the cyclization reaction; however, there was a corresponding increase in reaction time with lower catalyst loading. From these initial experiments, the conditions of entry 2 were selected as the standard conditions for future studies as it represents a compromise between catalyst loading and reaction times.

Table 1
RCM of model *N*-phenylacrylamide

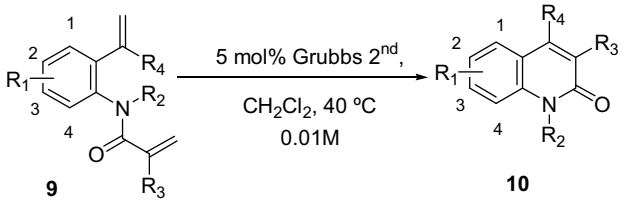


Entry	Catalyst loading (mol %)	Time (h)	Yield[a] (%)
1	10	2.5	95
2	5	7.5	88
3	2	96	91

[a] Isolated yields.

Having established the viability of using *N*-phenylacrylamide **7** in a RCM reaction, we next turned our attention at investigating the scope for this transformation. A variety of analogs of **7** were prepared varying the substituents around the *N*-phenylacrylamides core in order to explore the effects of the substituents on the reaction efficiency. The results of these studies are presented in Table 2, and several points from this table are worthy of further comment. Overall, the reaction is general in scope (with a few notable exceptions discussed below) providing good to excellent yields of the corresponding quinolinones. Substitution of the benzene ring (R_1) is well tolerated and we were pleased to observe high yields for the analogs incorporating bromine or the strongly electron-withdrawing CF_3 substituent (Table 2, entries 1 and 2, respectively). An added advantage of incorporating bromine as a substituent on the benzene ring is that it could potentially serve as a handle for further functionalization. Substitution at nitrogen (R_2) is well tolerated and provides excellent yields of the corresponding quinolinone (Table 2, entries 4–6). While Me and phenyl substitution at the acrylamide position (R_3) provided excellent yields of the corresponding quinolinone, the reaction completely failed when either a bromine or a CF_3 substituent was present. Vinyl bromides have been reported to be poor substrates for RCM, and this is consistent with our observation.[8] While there are several literature examples of vinyl chlorides undergoing successful RCM,[9,8b] the corresponding reaction with α-chloroacrylamide (Table 2, entry 11) was unresponsive to treatment

Table 2
RCM of substituted *N*-phenylacrylamides



Entry	R_1	R_2	R_3	R_4	Yield[a] (%)
1	4-CF_3	H	H	H	86
2	2-Br	H	H	H	82
3	4-Me	H	H	H	99
4	H	Me	H	H	98
5	H	iPr	H	H	95
6	H	Bn	H	H	99
7	H	H	Me	H	98
8	H	H	Ph	H	99
9	H	H	Br	H	NR[b]
10	H	H	CF_3	H	NR[b]
11	H	H	Cl	H	NR[b]
12	H	H	H	Me	99
13	H	H	H	Ph	38[c]
14	H	H	H	Bu	NR[b]

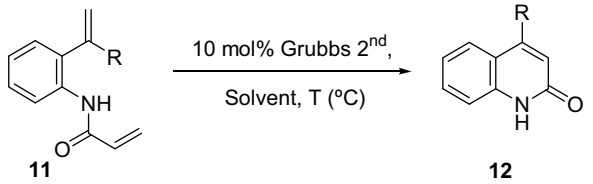
[a] Isolated yields.
[b] NR: No reaction.
[c] 10% Grubbs catalyst.

with Grubbs catalyst. Methyl substitution at the α-styrene position (R_4) of the molecule was well tolerated, giving nearly quantitative yields of quinolinone (entry 12). However, the corresponding phenyl analog proved sluggish, providing only a modest yield of the cyclized product (38%, entry 13) even with a higher catalyst loading (10%). Surprisingly, the *n*-butyl analog (entry 14) failed to furnish any of the desired products. Thus, the present reaction is sensitive to the steric demand of the R_4 substituent, and this suggests that the styrene olefin is the site of the initial reaction between the ruthenium catalyst and the substrate.[10]

The low reactivity of the phenyl analog prompted us to re-investigate the reaction conditions for this substrate. As outlined in Table 3, several modifications of the reaction conditions were evaluated, including modifying the solvent, temperature, performing the reaction under an atmosphere of ethylene, and delivery of the catalyst via syringe pump. From this exercise, the optimal conditions identified involved the use of benzene as the solvent with 10 mol % of catalyst at room temperature. This provided a modest yield of the desired heterocycle (53%). These conditions were used with the butyl analog and, with this substrate, only a low yield of the quinolinone was realized (11%).

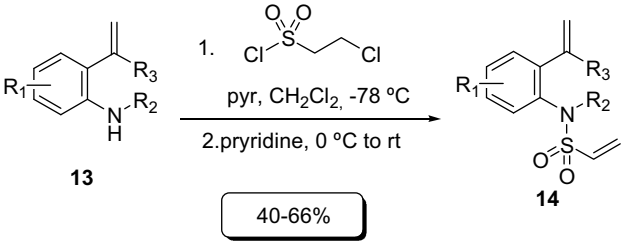
Having established the scope of the quinolinones formation reaction, we then examined the applicability of this chemistry toward the synthesis of benzothiazine 1,1-dioxides.[11] The required *N*-phenylethylenesulfonamides were prepared according to the reaction conditions described in Scheme 2, which are based on modified literature procedures.[12] After some experimentation, the optimal reaction

Table 3
Optimization studies



Entry	Solvent	R	*T* (°C)	Yield[a] (%)
1	CH_2Cl_2	Ph	22	17
2[b]	CH_2Cl_2	Ph	40	38
3[c]	CH_2Cl_2	Ph	40	38
4	CH_2Cl_2	Ph	22	16
5	C_6H_6	Ph	80	36
6	C_6H_6	Ph	22	53
7	C_6H_6	Bu	22	11

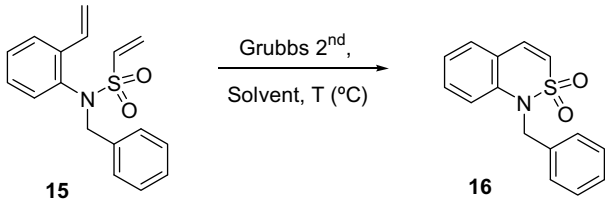
[a] Isolated yields.
[b] Syringe pump addition.
[c] Ethylene atmosphere.



Scheme 2. Preparation of *N*-phenylethylenesulfonamides.

conditions identified were to treat the corresponding anilines[13] with 2-chloroethanesulfonyl chloride in the presence of pyridine at −78 °C. The reaction mixture is then warmed to 0 °C followed by the addition of a second equivalent of pyridine, and then the reaction mixture is warmed to room temperature. The corresponding unsaturated sulfonamides were thus obtained in moderate to good yields following standard work-up and purification. With the *N*-phenyleth-

Table 4
RCM of model *N*-phenylethylenesulfonamide



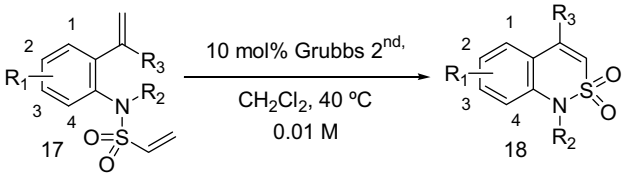
Entry	Solvent	Catalyst loading (mol %)	Yield (% conv)
1	CH_2Cl_2	10	85[a]
2	CH_2Cl_2	5	(54)[b]
3	C_6H_6	10	(0)[b]

[a] Isolated yield.
[b] Percent conversion estimated by ^1H NMR analysis of the crude reaction mixture.

ylenesulfonamide in hand, we next turned our attention at exploring the ability of these compounds to undergo RCM reactions. The first reaction parameter examined was the effect of catalyst loading on the RCM reaction of substrate **15** as shown in Table 4. We were pleased to see that an exposure of diene **15** to 10 mol % of Grubbs catalyst provided an 85% isolated yield of the benzothiazine 1,1-dioxide product **16**. Lowering the catalyst loading to 5 mol % was found to have a significant negative impact on the product yield, in contrast to what was observed in the quinolinone series. When benzene was employed as the reaction solvent, the reaction mixture turned black within 15 min (a sign of catalyst decomposition) and none of the expected product was detected. From these initial studies, the conditions of entry 1 from Table 4 were selected as the standard conditions for further studies.

The scope of the *N*-phenylethylenesulfonamide RCM chemistry presented in Table 5, in general, mirrors the results with the quinolinone system. As illustrated in this table, benzene substitution (R_1) is well tolerated as both electron-withdrawing and electron-donating substituents give excellent yields of the desired product (Table 5, entries 1–6). Similar to the quinolinone findings, substitution on nitrogen (R_2) with alkyl, benzyl, and substituted benzyl derivatives smoothly proceeded to give excellent yields of the corresponding benzothiazine 1,1-dioxide products. While a methyl substituent at the α-styryl position (R_3) allows for the smooth conversion to the cyclized product (92%), a phenyl substituent at this position completely shuts down the RCM reaction (Table 5, entry 14), similar to what was observed with the quinolinone series (Table 2, entries 13 and 14).

Table 5
RCM of substituted *N*-phenylethylenesulfonamides



Entry	R_1	R_2	R_3	Yield[a] (%)
1	2-Me	H	H	87
2	4-Me	H	H	95
3	2-Cl	H	H	82
4	4-OMe	H	H	Quant.
5	4-CF_3	H	H	85
6	2,4-Cl	H	H	75
7	H	H	H	Quant.
8	H	Me	H	86
9	H	Bn	H	85
10	H	4-CN–Bn	H	82
11	H	4-Br–Bn	H	96
12	H	4-CF_3–Bn	H	94
13	H	H	Me	92
14	H	H	Ph	NR[b]

[a] Isolated yields.
[b] NR: No reaction.

In summary, we have presented an efficient RCM approach for the synthesis of highly functionalized quinolinones and benzothiazine 1,1-dioxides. The method is general in scope and offers the opportunity for the convenient synthesis of functionalized systems. The generality and scope of the method presented herein should find application in the synthesis of these ring systems. To date, the main limitation in the RCM of these substrates is the narrow scope at substitution at the α-styryl and α-acrylamide positions of the molecule. Studies aimed at overcoming these limitations are in progress and will be disclosed in due course.

Acknowledgment

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