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PREPARATION OF *N*-SULFONYL-2-QUINOLINONE USING RING-CLOSING METATHESIS(RCM)

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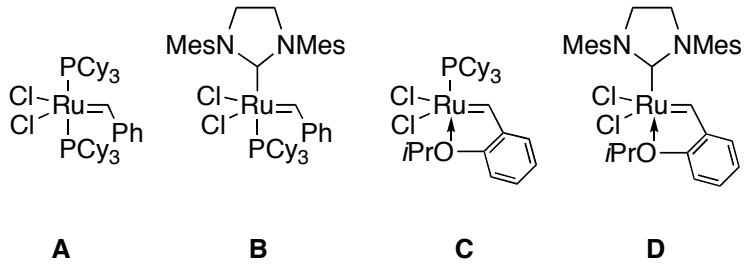
Abstract – An efficient method for the preparation of *N*-sulfonyl-2-quinolinone using ring-closing metathesis (RCM) is described.

INTRODUCTION

It is still a challenge to develop more efficient methodologies and strategies for producing heterocycles with the desired substituents and functional groups, despite the considerable amount of effort that has been expended in this area.[1]

Metathesis has opened a new field of organic chemistry since it was introduced in the 1970s. Recent ruthenium catalysts (**A**[2], **B**[3], **C**[4], and **D**[5] Figure), which were developed by Grubbs, Hoveyda, and their respective co-workers, are compatible with a variety of functional groups, easy to handle and, now commercially available.[6]



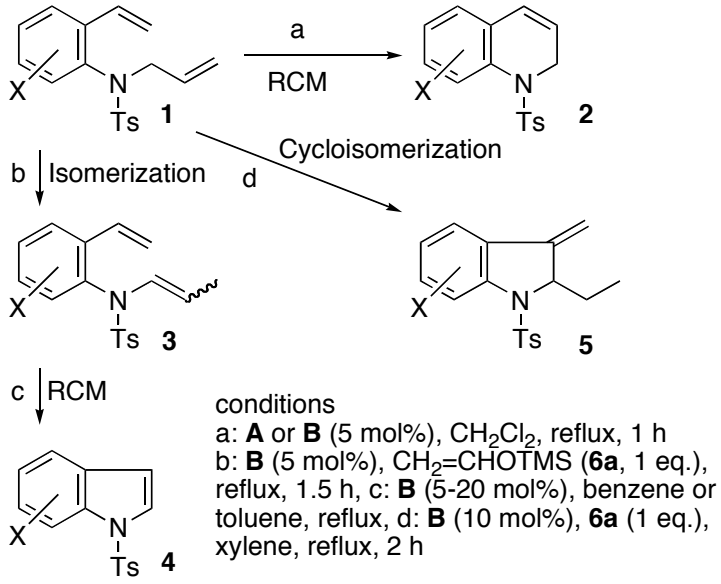
A **B** **C** **D**

Figure. Ruthenium Carbene Catalysts.

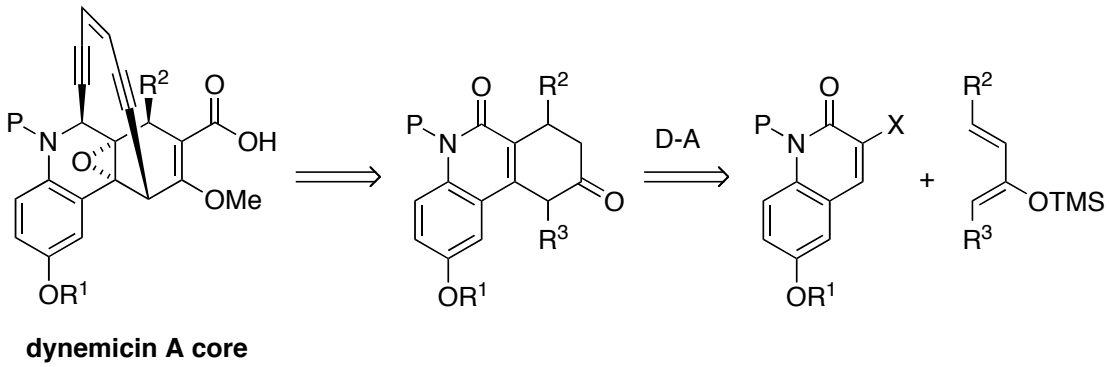
We have been investigating the feasibility of using metathesis to prepare heterocyclic compounds and its application to the synthesis of bioactive natural products. Recently, we found that *N*-allyl-*o*-vinylaniline (**1**) gave 1,2-dihydroquinoline (**2**) by normal RCM, and developed silyl enol ether - ene metathesis for the

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

novel synthesis of 4-silyloxy-1,2-dihydroquinoline, and thus demonstrated a convenient entry to quinolines and 1,2,3,4-tetrahydroquinoline.[7f,k] We also found a novel selective isomerization of terminal olefin and a cycloisomerization of 1,6-dienes, using ruthenium carbene catalyst and silyl enol ether, which represented a new synthetic route to a series of substituted indoles (**4**) and 3-methylene-2,3-dihydroindoles (**5**) (Scheme 1).[7h,l,n] We now report our novel preparation of *N*-sulfonyl-2-quinolinones using RCM.



Scheme 1. Synthesis of **2**, **4**, **5** from **1**.



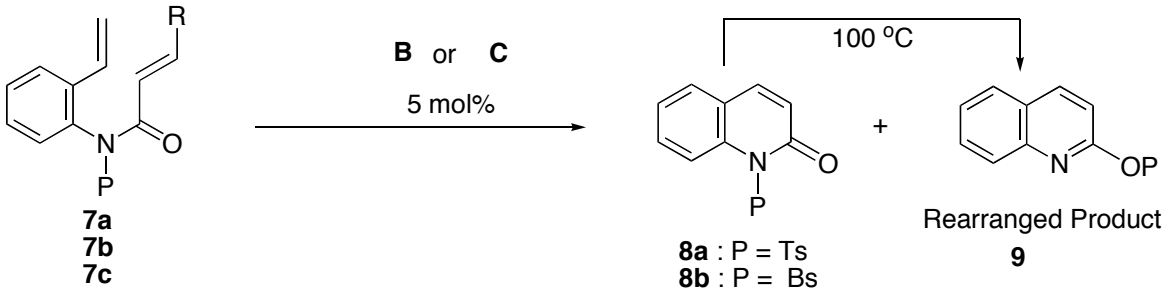
Scheme 2. Diels-Alder Reaction for Dynemicin A Core.

2-Quinolones are valuable intermediates in organic synthesis[8] and *N*-sulfonyl-2-quinolinones are difficult to prepare by conventional methods because *O*-sulfonyl-2-quinolinones would be obtained preferentially instead of *N*-sulfonylation. In our previous work on the synthesis of dynemicin A,[9] we found that *N*-protected-2-quinolinone derivatives are good dienophiles for the Diels-Alder reaction (Scheme 2). Theoretically, *N*-sulfonyl-2-quinolinones should be better dienophiles than *N*-methoxycarbonyl or

N-methoxymethyl derivatives. However, we could not prepare *N*-sulfonyl-2-quinolinones using conventional methods.

RESULTS AND DISCUSSION

Dienes (**7**) were prepared by condensation of the corresponding *N*-protected aniline and acid chloride. When catalyst **B** was used for RCM of **7a** under the standard conditions, no cyclized product was obtained and the starting material was recovered (Entry 1). Thus, instead of catalyst **B**, catalyst **C** was used under the same reaction conditions. The *N*-tosyl-2-quinolinone (**8a**) was obtained in trace amounts. When the reaction temperature was raised to 100 °C, *N*-tosyl-2-quinolinone (**8a**) was obtained in 56% yield, while rearranged product (**9**) was also obtained in 32% yield (Entry 3). In Entry 4, the reaction temperature was reduced to 80 °C, the reaction mixture was stirred for 4 h, and the desired *N*-tosyl-2-quinolinone (**8a**) was obtained in quantitative yield. Thermal rearrangement of **8** to **9** occurred at 100 °C quantitatively without any catalyst. Compound (**9**) should be a useful substrate for the synthesis of 2-substituted quinolines by a coupling reaction.



Entry	Substrate			Catalyst	Conditions			Product (%)	Remark
		R	P		Temp. (°C)	Solvent	Time (h)		
1	**7a**	H	Ts	**B**	50	CH_2Cl_2	1	NR	-
2	**7a**	H	Ts	**C**	50	CH_2Cl_2	1	**8a** (trace)	-
3	**7a**	H	Ts	**C**	100	toluene	4	**8a** (56)	rearrange 32 %
4	**7a**	H	Ts	**C**	80	toluene	4	**8a** (95)	-
5	**7b**	Me	Ts	**C**	80	toluene	4	**8a** (74)	STM 20%
6	**7c**	H	Bs	**C**	80	toluene	5	**8b** (90)	-

Table. Preparation of *N*-Sulfonyl-2-quinolinone.

N-Crotonoyl-*N*-tosylaminostyrene (**7b**) was subjected to the same reaction conditions as in Entry 4 and gave *N*-tosyl-2-quinolinone (**8a**) in 74% yield (Entry 5). RCM of **7c** was accomplished within 5 h using catalyst **C**, and *N*-benzenesulfonyl-2-quinolinone (**8b**) was obtained in 90% yield (Entry 6).

Thus, the development of a novel method for preparing *N*-sulfonyl-2-quinolinone was achieved by RCM using a well-defined Hoveyda catalyst (**C**) and dienes at 80 °C. The reaction proceeded efficiently under mild conditions. Further studies of the D-A reaction using *N*-sulfonyl-2-quinolinone are currently in progress in our laboratory.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (cm^{-1}) were recorded using a KBr or NaCl pellet. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, and DMSO-d_6 unless otherwise noted, at 400 MHz, with TMS as an internal standard. E. Merck silica gel 60 was used for column chromatography, and E. Merck precoated TLC plates, silica gel F_{254}, were used for preparative thin layer chromatography. The organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4.

***N*-*p*-Toluenesulfonyl-2-quinolinone (8a).**

To a solution of *N*-*p*-toluenesulfonyl-2-aminostyrene (100 mg, 0.37 mmol) and Et_3N (0.07 mL, 0.55 mmol) in 10 mL of CH_2Cl_2 under an Ar atmosphere, was added acryloyl chloride (0.03 mL, 0.40 mmol). The solution was stirred at rt for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:Acetone = 3:1) to give 110 mg (92%) of *N*-acryloyl-*N*-*p*-toluenesulfonyl-2-aminostyrene as a white solid. To a solution of *N*-acryloyl-*N*-*p*-toluenesulfonyl-2- aminostyrene (60 mg, 0.18 mmol) in 18 mL of toluene under an Ar atmosphere, was added catalyst **C** (6.4 mg, 0.008 mmol). The mixture was stirred at 80 °C for 4 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) followed by recrystallization from AcOEt to give 49 mg (95%) of **8a** as colorless crystals. mp 165 °C; ^1H NMR ($CDCl_3$) δ 8.64 (1H, d, *J* = 8.8 Hz), 8.00 (2H, d, *J* = 8.4 Hz), 7. 75 (2H, d, *J* = 9.5 Hz), 7.50 (1H, d, *J* = 7.7 Hz), 7.33 (3H, d, *J* = 7.9 Hz), 6.38 (1H, d, *J* = 9.3 Hz), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 161.9, 145.3, 141.8, 137.5, 136.6, 130.4, 129.4, 128.8, 128.7, 124.5, 122.2, 121.7, 119.2, 21.7; IR (KBr) 3451, 3051, 2921, 1681, 1591, 1360; LRMS (EI) m/z 341 [100].

***N*-Benzenesulfonyl-2-quinolinone (8b).**

To a solution of *N*-benzenesulfonyl-2-aminostyrene (300 mg, 1.14 mmol) and Et_3N (0.24 mL, 1.71 mmol) in 10 mL of CH_2Cl_2 under an Ar atmosphere, was added acryloyl chloride (0.10 mL, 1.25 mmol). The solution was stirred at rt for 1 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:Acetone = 3:1) to give 335 mg (95%) of

N-acryloyl-*N*-benzenesulfonyl-2-aminostyrene as a white solid. To a solution of *N*-acryloyl-*N*-benzenesulfonyl-2-aminostyrene (90 mg, 0.27 mmol) in 27 mL of toluene under an Ar atmosphere, was added catalyst **C** (8.6 mg, 0.014 mmol). The mixture was stirred at 80 ºC for 5 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) followed by recrystallization from AcOEt to give 73 mg (90%) of **8b** as colorless crystals. mp 144 ºC; ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, *J* = 8.8 Hz), 8.12 (2H, d, *J* = 8.3 Hz), 7.65 (1H, dd, *J* = 7.1, 7.8 Hz), 7.50-7.59 (5H, m), 7.33 (1H, dd, *J* = 7.3, 7.6 Hz), 6.38 (1H, d, *J* = 9.7 Hz); ^{13}C NMR ($CDCl_3$) δ 161.9, 141.9, 139.7, 137.5, 134.1, 135.0, 128.9, 128.8, 128.7, 124.7, 122.2, 121.7, 119.2; IR (KBr) 3451, 3060, 2921, 1666, 1591, 1448, 1363; LRMS (EI) m/z 285 [100].

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