Pergamon

Tetrahedron 58 (2002) 5075–5080

TETRAHEDRON

Reaction of different α-sulfonyl acetamides with methyl acrylate

Meng-Yang Chang,[a] Shui-Tein Chen[a,*] and Nein-Chen Chang[b,*]

[a]*Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan, ROC*
[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC*

Received 1 April 2002; accepted 30 April 2002

Abstract—The base-induced tandem-coupling/cyclization reactions of various α-sulfonyl acetamide derivatives **A** with methyl acrylate differentiated between two different pathways to form α-sulfonyl analogs of glutarimides **B** and 2-hydroxycyclohexenecarboxylic acid derivatives **C** in different ratios. The reaction of α-sulfonyl acetamide dianion with methyl acrylate depended on three factors: the stability of the dianion, concentration of methyl acrylate and the structure of sufonyl and amide substituents. By changing the reaction conditions, we efficiently controlled the cycloaddition reaction to synthesize the desired product, each of which has potential biological activities. A ring closure mechanism is proposed for the reactions.

1. Introduction

Michael reactions are very useful and powerful tools in synthetic chemistry.[1] In general, Michael addition proceeds by process of deprotonation, conjugate addition, and protonation of the conjugate base of adducts. Because these steps are reversible, it is imperative to choose reaction conditions and substituents judiciously to drive the equilibria toward formation of products as the results of thermodynamic control.[2] Reactions of α,β-unsaturated carbonyl systems involve a tandem process of first a double Michael addition followed by a Dieckmann cyclization. While this indicates double Michael addition originating from the same donor carbon atom, the serial version has also been developed. There has been several reports of a sequence of two Michael additions followed by formal [3+3] cycloaddition reaction.[3,4] These reports prompted us to investigate the base-induced addition of α-sulfonyl acetamide to α,β-unsaturated carbonyl systems, where the 1,4-addition products are expected because α-sulfonyl acetamide forms a stable dianion intermediate.[2] The cycloaddition reaction of *N*-benzyl α-toluenesulfonyl acetamide with α- or β-substituted unsaturated esters have produced various glutarimides in good yields.[3d]

In this paper, we report on factors for the optimal conditions for a tandem double 1,4-addition-Dieckmann condensation and 1,4-addition-cyclization of α-sulfonyl acetamide with methyl acrylate that lead to analogs of α-sulfonyl glutarimides **B** and 2-hydroxycyclohexenecarboxylic acid derivatives **C** (see Fig. 1). The skeletal frameworks of **B**[5,6] and **C**[7,8] are structurally similar to clinical drugs and are potentially

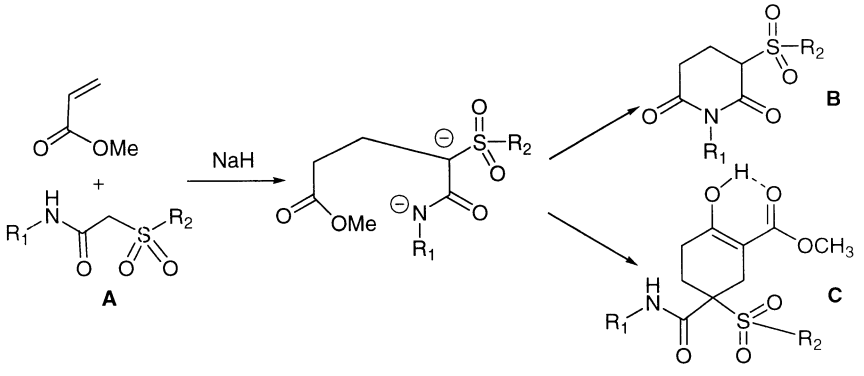
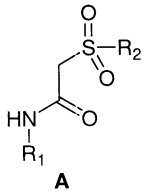


Figure 1. Reaction of different α-sulfonyl acetamides **A** with methyl acrylate.

Keywords: cycloaddition reaction; α-sulfonyl acetamide dianion; methyl acrylate; glutarimides.
* Corresponding authors. Fax: +886-2-27883473; e-mail: bcchen@gate.sinica.edu.tw

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00475-1



A1-1 R_1=Bn, R_2=Tol
A1-2 R_1=Bn, R_2=Ph
A1-3 R_1=Bn, R_2=Me
A1-4 R_1=Bn, R_2=*n*-Bu
A2-1 R_1=Tryptaminyl, R_2=Tol
A3-1 R_1=*t*-Bu, R_2=Tol
A3-2 R_1=*t*-Bu, R_2=Ph
A3-3 R_1=*t*-Bu, R_2=Me
A3-4 R_1=*t*-Bu, R_2=*n*-Bu
A4-1 R_1=Ph, R_2=Tol
A4-2 R_1=Ph, R_2=Ph
A4-3 R_1=Ph, R_2=Me

A

Figure 2. Different substituted α-sulfonyl acetamide **A**.

biologically active; the multiple potential biological activities of similar structures have attracted many synthetic efforts. Furthermore, the reaction sequence provides insights into the mechanism for constructing six-membered ring using methyl acrylate and *N*-substituents α-substituents sulfonyl acetamides as the starting materials.

2. Results and discussion

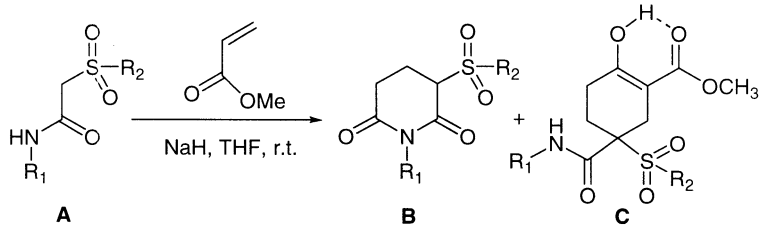
2.1. Reaction of α-sulfonyl acetamides with methyl acrylate

We investigated the reactions of sulfonyl acetamides **A** having various *N*-substituents (R_1) α-substituents (R_2) with methyl acrylate to yield products **B** and **C** via the cycloaddition reactions in basic condition. Compounds **A** were prepared by known procedures.[3d] Deprotonation of compounds **A** using sodium hydride (2.2 equiv.) in tetrahydrofuran at room temperature led to the dianions intermediate state. The cycloaddition reactions of the dianions **A** (see Fig. 2) with methyl acrylate proceeded via pathways a–c to yield products **B** and **C** as shown in Table 1 and Scheme 1.

2.2. Factors in the selectivity of the cycloaddition reactions

The investigation began with a cycloaddition reaction of a typical **A1-1** with methyl acrylate. After dianion **I** was generated by the action of sodium hydride on **A1-1** at room temperature, methyl acrylate (1.3 equiv.) was added in tetrahydrofuran (50 mL) for ca. 8.5 h. The ratio of **B** and **C** was 4:1 with 78% overall yield. When the rate of addition (mL/min) and the concentration (g/mL) of methyl acrylate in tetrahydrofuran were changed from 1/10 and 1/50 to 1/20 and 1/100, the yield of products increased to 90% of essentially **B**. The more diluted the concentration of methyl acrylate in tetrahydrofuran added more slowly into the reaction mixture increased the lifetime of dianion **III** allowing intramolecular cyclization (pathway b). In other words,

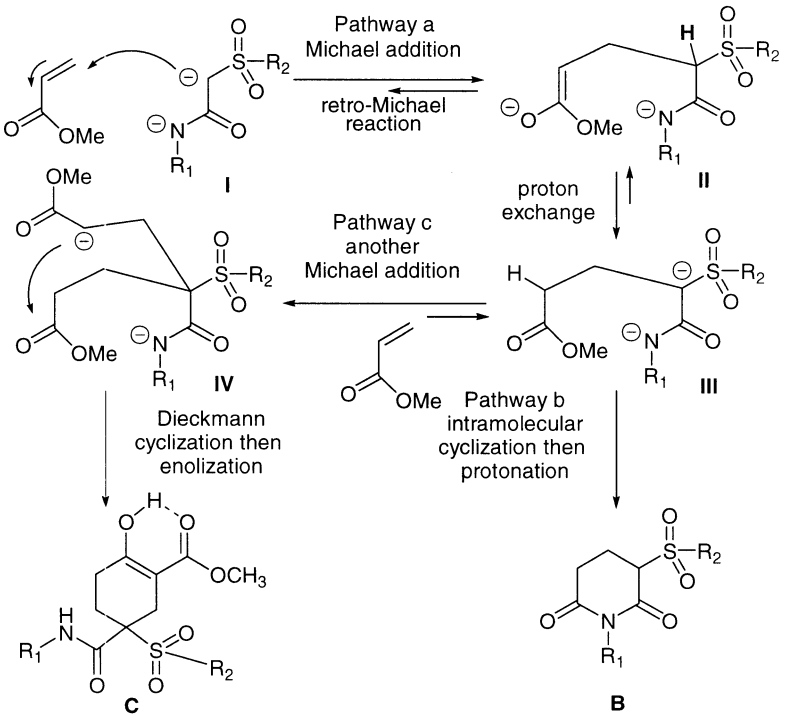
Table 1. Cycloaddition reactions of dianions **A** with methyl acrylate



A **B** **C**

Reaction no.	A	R_1, R_2	Rate, concentartion, equiv. of methyl acrylate (mL/min, g/mL, equiv.)	Ratio[a] (**B**/**C**)	Yield[b] (**B**+**C**) (%)
1	**A1-1**	Bn, Tol	1/10, 1/50, 1.3	4:1	78
2	**A1-1**	Bn, Tol	1/10, 1/100, 1.3	9:1	82
3	**A1-1**	Bn, Tol	1/20, 1/100, 1.3	1:0	90
4	**A1-2**	Bn, Ph	1/10, 1/50, 1.3	3:1	76
5	**A1-2**	Bn, Ph	1/20, 1/100, 1.3	10:1	86
6	**A1-3**	Bn, Me	1/10, 1/50, 1.3	1:0	66
7	**A1-4**	Bn, *n*-Bu	1/10, 1/50, 1.3	1:0	69
8	**A2-1**	Tryp., Tol	1/10, 1/50, 1.3	3:1	72
9	**A2-1**	Tryp., Tol	1/20, 1/100, 1.3	8:1	80
10	**A3-1**	*t*-Bu, Tol	1/10, 1/50, 1.3	0:1	46[c]
11	**A3-1**	*t*-Bu, Tol	1/20, 1/100, 1.3	0:1	54[c]
12	**A3-2**	*t*-Bu, Ph	1/10, 1/50, 1.3	0:1	43[c]
13	**A3-2**	*t*-Bu, Ph	1/10, 1/100, 1.3	0:1	50[c]
14	**A3-3**	*t*-Bu, Me	1/10, 1/50, 1.3	0:1	42[c]
15	**A3-3**	*t*-Bu, Me	1/3, 1/10, 10	0:1	73
16	**A3-4**	*t*-Bu, *n*-Bu	1/10, 1/50, 1.3	0:1	40[c]
17	**A3-4**	*t*-Bu, *n*-Bu	1/3, 1/10, 10	0:1	70
18	**A4-1**	Ph, Tol	1/10, 1/50, 10	No reaction	
19	**A4-2**	Ph, Ph	1/10, 1/50, 10	No reaction	
20	**A4-3**	Ph, Me	1/10, 1/50, 10	No reaction	

[a] The product ratio was adjusted based on isolated products.
[b] All yields were based on **A** confirmed.
[c] **A** was recovered in 30–40% yield.



Scheme 1. Stepwise formation of compounds **B** and **C**.

the diluted condition showed preferred selectivity for compounds **B**. Therefore, the ratio of **B** and **C** depended on the rate of addition (mL/min) and the concentration (g/mL) of methyl acrylate in tetrahydrofuran in the reaction with **A1**-**1**. These reaction conditions are described in Table 1.

When R_1 was Bn or tryptaminyl, we detected two kinds of cycloadducts **B** and **C** (reactions 1, 2, 4, 5, 8, and 9). Whereas, when R_2 was Tol (reaction 3) and when R_2 was Ph (reaction 5), compounds **B** were the only major products. Furthermore, when the R_2 group was Me (reaction 6) or *n*-Bu (reaction 7), we have no need to control rate and concentration of methyl acrylate, compounds **B** were the sole products produced in moderate yield. We believe that the differences in R_2 substituents, between aromatic and aliphatic groups, affected the reaction pathways, between pathways b and c.

In order to synthesize **C** as major products, we changed the R_1 substituents to inhibit the preference for pathway b. When R_1=*t*-Bu, we obtained **C** as the sole products (reactions 10–17), varying the rate of addition and the concentration of methyl acrylate did not influenced the product ratio, and 30–40% of **A** was recovered after the reaction. The *t*-butyl substituent on dianion **III** was too bulky to allow the formation of **B** via pathway b and the subsequent addition of dianion **III** to another methyl acrylate followed by the Dieckmann condensation and enolization yielded **C** via pathway c. The appearance of unreacted **A** in the product mixture indicated insufficient amount of methyl acrylate in the reaction system. When the amount of methyl acrylate was increased from 1.3 to 10 equiv., the product yields improved from 40–54 to 70–73% (reactions 15 and 17). The reaction of substrates having bulky R_1=*t*-Bu group preferred pathway c to yield **C** without need to control rate and concentration of methyl acrylate.

When R_1=Ph, we found that **A** did not react with methyl acrylate (reactions 18–20). The R_1=Ph group of dianion **III** decreased the nucleophilicity of nitrogen atom on **A**, and the reaction preferred retro-Michael reaction to recover **A**. Furthermore, R_2 group of **A** was another important factor influencing the reaction pathways and resultant products.

2.3. Proposed mechanisms leading to compounds B and C

The proposed reaction mechanisms of α-sulfonyl acetamides **A** with methyl acrylate are shown in Scheme 1.

First, the formed dianion **I** attacks the 4-position of the methyl acrylate to produce dianion **II** by Michael addition reaction (pathway a). From this state, dianion **II** has two possible pathways: the reverse reaction of retro-Michael reaction and the forward reaction of proton exchange. In the reverse reaction, the less stable dianion **II** goes back to the more stable dianion **I** via a retro-Michael reaction. In the forward reaction, the less stable dianion **II** exchanges proton with acidic hydrogen to form dianion **III**. The dianion **III** is a key intermediate in the mechanism. Under proper rate of addition and in dilute concentration of methyl acrylate, dianion **III** proceeds with the ring closure reaction. Thus, pathway b produces the skeleton of glutarimides **B** by intramolecular cyclization of dianion **III**. However, when the substrates have bulky R_1 groups, the ring closure reaction of dianion **III** is blocked. Therefore, in pathway c, dianion **III** proceeds by double Michael addition to produce dianion **IV**. Dianion **IV** participates in Dieckmann

cyclization and enolization (O*H* ca. δ 12.0) to yield α-sulfonyl acetamide derivatives **C**.

3. Conclusion

The base-induced tandem-coupling/cyclization reactions of various α-sulfonyl acetamide derivatives with methyl acrylate differentiate between two different pathways to form α-sulfonyl analogs of glutarimides **B** and 2-hydroxycyclohexenecarboxylic acid derivatives **C** in different ratios. The stability of dianions (**I**–**IV**), the substituent groups (R_1 and R_2) on **A**, and the rate of addition and the concentration of methyl acrylate influenced the direction of cycloaddition reaction to produce two different six-membered products. By changing the reaction conditions we can efficiently control the cycloaddition reaction to produce the desired skeleton, each of which has various potential biological activities. A ring closure mechanism leading to the two different cycloadducts is proposed.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Organic solution of products was dried with anhydrous magnesium sulfate before concentration in vacuo. These crude products were purified using preparative TLC or column chromatography on silica gel. All reported temperatures were uncorrected.

4.2. General preparation of α-sulfonyl acetamides A

Chloroacetyl chloride (10.6 mmol) in tetrahydrofuran (20 mL) was added to a solution of amine (10.0 mmol) and triethylamine (10.5 mmol) in tetrahydrofuran (30 mL) while in ice bath and stirred for 30 min. The reaction mixture was further stirred at room temperature for 4 h, and concentrated under reduced pressure. Water (20 mL) was added to the residue, and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Without further purification, the crude product was refluxed with *p*-toluenesulfonic acid sodium salt (16.5 mmol) in dioxane (70 mL) and water (70 mL) for 10 h, and concentrated under reduced pressure. Water (20 mL) was added to the residue, and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization from hexane and ethyl acetate (ca. 3/1) yielded pure **A**. **A** was gave in 80–90% yield.

4.3. General cycloaddition reaction of α-sulfonyl acetamides A with methyl acrylate

A solution of α-sulfonyl acetamide **A** (1.0 mmol) in tetrahydrofuran (10 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 2.2 mmol) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at room temperature for 5 min, a solution of methyl acrylate (112 mg, 1.3 mmol) in tetrahydrofuran was added. The resulting mixture was stirred at room temperature under different reaction conditions as shown in the Table 1, and then quenched with saturated ammonium chloride solution (1 mL), and concentrated under reduced pressure. Water (20 mL) was added to the residue, and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on column chromatography with silica gel (hexane/ethyl acetate=4/1–2/1) yielded skeletons of **B** and **C**. The ratio of **B** and **C** is shown in Table 1.

4.4. Spectra data of B and C

4.4.1. [R_1=Bn, R_2=Tol]: 1-Benzyl-3-(4-methylphenylsulfonyl)-2,6-azinanedione. Mp=66–69°C; IR ($CHCl_3$) 1728, 1677 cm^{-1}; ESI-MS: $C_{19}H_{20}NO_4S$ *m/z* (%)=91 (100), 358 (M^++1, 55); HRMS (ESI, M^++1) calcd for $C_{19}H_{20}NO_4S$ 358.1114, found 358.1112; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J*=8.1 Hz, 2H), 7.32–7.25 (m, 7H), 5.03 (d, *J*=13.8 Hz, 1H), 4.86 (d, *J*=13.8 Hz, 1H), 4.06 (br s, 1H), 3.38–3.20 (m, 1H), 2.82–2.68 (m, 2H), 2.43 (s, 3H), 2.40–2.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.66, 164.65, 145.59, 135.28, 134.36, 129.69 (2×), 128.94 (2×), 128.57 (2×), 128.24 (2×), 127.40, 65.62, 43.38, 29.15, 21.71, 17.62; Anal. calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36. Found: C, 63.90; H, 5.44.

4.4.2. Methyl 5-benzylcarbamoyl-2-hydroxy-5-(4-methylphenylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=160–162°C; IR ($CHCl_3$) 3421, 3025, 1741, 1674 cm^{-1}; ESI-MS: $C_{23}H_{26}NO_6S$ *m/z* (%)=91 (100), 444 (M^++1, 44); HRMS (EI, M^++1) calcd for $C_{23}H_{25}NO_6S$ 443.1404, found 443.1405; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.11 (s, 1H), 7.49 (d, *J*=8.4 Hz, 2H), 7.39–7.21 (m, 7H), 7.15 (br s, 1H), 4.49 (dd, *J*=6.0, 14.7 Hz, 1H), 4.37 (dd, *J*=5.7, 14.7 Hz, 1H), 3.72 (s, 3H), 3.00 (d, *J*=15.6 Hz, 1H), 2.84 (d, *J*=15.6 Hz, 1H), 2.53–2.36 (m, 3H), 2.43 (s, 3H), 2.23–2.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.59, 170.27, 164.98, 145.63, 137.38, 131.40, 129.78 (2×), 129.70 (2×), 128.70 (2×), 128.15 (2×), 127.66, 94.04, 70.15, 51.70, 44.48, 26.25, 25.40, 24.63, 21.71; Anal. calcd for $C_{23}H_{25}NO_6S$: C, 62.29; H, 5.68. Found: C, 62.37; H, 5.71.

4.4.3. [R_1=Bn, R_2=Ph]: 1-Benzyl-3-(4-phenylsulfonyl)-2,6-azinanedione. Viscous oil; IR ($CHCl_3$) 1733, 1669 cm^{-1}; ESI-MS: $C_{18}H_{18}NO_4S$ *m/z* (%)=91 (100), 344 (M^++1, 61); HRMS (ESI, M^++1) calcd for $C_{18}H_{18}NO_4S$ 344.0957, found 344.0960; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 3H), 7.50–7.45 (m, 3H), 7.33–7.24 (m, 4H), 5.03 (d, *J*=14.0 Hz, 1H), 4.86 (d, *J*=14.0 Hz, 1H), 4.08 (br s, 1H), 3.32–3.22 (m, 1H), 2.83–2.73 (m, 2H), 2.39–2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.73, 164.69, 137.53, 136.39, 134.52, 129.15 (3×), 129.06 (2×), 128.85, 128.39, 127.57 (2×), 65.67, 43.48, 29.23, 17.62; Anal. calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99. Found: C, 63.03; H, 5.07.

4.4.4. Methyl 5-benzylcarbamoyl-2-hydroxy-5-(4-phenylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=146–147°C; IR ($CHCl_3$) 3426, 3029, 1733, 1677 cm^{-1}; ESI-MS: $C_{22}H_{24}NO_6S$ *m/z* (%)=91 (100), 430 (M^++1, 18); HRMS (ESI, M^++1) calcd for $C_{22}H_{24}NO_6S$ 430.1325, found 430.1323; ^1H NMR (400 MHz, $CDCl_3$): δ 12.08 (s, 1H), 7.62–7.24 (m, 10H), 7.08 (br s, 1H), 4.47 (dd, *J*=6.1, 14.6 Hz, 1H), 4.36 (dd, *J*=5.6, 14.6 Hz, 1H), 3.71 (s, 3H), 3.00 (dd, *J*=1.2, 15.6 Hz, 1H), 2.84 (d, *J*=15.6 Hz, 1H), 2.52–2.35 (m, 3H), 2.21–2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.66, 170.39, 164.95, 137.45, 134.60, 134.50, 129.90 (2×), 129.32, 129.10, 128.84 (2×), 128.47, 128.26, 127.79, 94.04, 70.29, 51.74, 44.53, 26.24, 25.40, 24.65; Anal. calcd for $C_{22}H_{23}NO_6S$: C, 61.52; H, 5.40. Found: C, 61.66; H, 5.49.

4.4.5. [R_1=Bn, R_2=Me]: 1-Benzyl-3-(4-methylsulfonyl)-2,6-azinanedione. Viscous oil; IR ($CHCl_3$) 1741, 1661 cm^{-1}; ESI-MS: $C_{13}H_{16}NO_4S$ *m/z* (%)=91 (100), 154 (91), 282 (M^++1, 95); HRMS (ESI, M^++1) calcd for $C_{13}H_{16}NO_4S$ 282.0801, found 282.0800; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5H), 5.04 (d, *J*=14.1 Hz, 1H), 4.96 (d, *J*=14.1 Hz, 1H), 4.01 (t, *J*=5.5 Hz, 1H), 3.16 (s, 3H), 3.15–3.08 (m, 1H), 2.74–2.67 (m, 2H), 2.37–2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.44, 165.80, 136.21, 128.85, 128.53 (3×), 127.67, 63.83, 43.63, 41.98, 29.46, 16.16; Anal. calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37. Found: C, 55.58; H, 5.48.

4.4.6. [R_1=Bn, R_2=*n*-Bu]: 1-Benzyl-3-(4-*n*-butylsulfonyl)-2,6-azinanedione. Mp=66–67°C; IR ($CHCl_3$) 1743, 1672 cm^{-1}; ESI-MS: $C_{16}H_{22}NO_4S$ *m/z* (%)=91 (100), 202 (15), 324 (M^++1, 64); HRMS (ESI, M^++1) calcd for $C_{16}H_{22}NO_4S$ 324.1271, found 324.1275; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 5.03 (d, *J*=14.1 Hz, 1H), 4.96 (d, *J*=14.1 Hz, 1H), 4.01 (br s, 1H), 3.32–3.25 (m, 2H), 3.16–3.08 (m, 1H), 2.74–2.68 (m, 2H), 2.35–2.25 (m, 1H), 1.82 (m, 2H), 1.51–1.41 (m, 2H), 0.95 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.60, 165.95, 136.29, 128.50, 128.32 (2×), 127.60 (2×), 61.80, 53.58, 43.59, 29.51, 23.79, 21.61, 16.21, 13.49; Anal. calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54. Found: C, 59.56; H, 6.67.

4.4.7. [R_1=Tryptaminyl, R_2=Tol]: 1-{2-(1*H*-benzo[*b*]-azol-3-yl)ethyl}-3-(4-methylphenylsulfonyl)-2,6-azinanedione. Mp=177–179°C; IR ($CHCl_3$) 3025, 1667 cm^{-1}; ESI-MS: $C_{22}H_{23}N_2O_4S$ *m/z* (%)=411 (M^++1, 100); HRMS (EI, M^+) calcd for $C_{22}H_{22}N_2O_4S$ 410.1302, found 410.1305; ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (br s, 1H), 7.72 (d, *J*=8.4 Hz, 2H), 7.70 (d, *J*=6.3 Hz, 1H), 7.36 (d, *J*=8.4 Hz, 2H), 7.33 (d, *J*=7.8 Hz, 1H), 7.18–7.11 (m, 2H), 7.02 (d, *J*=2.4 Hz, 1H), 4.11–4.02 (m, 3H), 3.28–3.15 (m, 1H), 2.98 (t, *J*=7.8 Hz, 2H), 2.75–2.60 (m, 2H), 2.45 (s, 3H), 2.23–2.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.64, 164.77, 145.73, 136.05, 134.84, 129.84 (2×), 128.97 (2×), 127.46, 122.33, 121.93, 119.33, 118.87, 112.28, 111.06, 65.64, 40.95, 29.25, 23.31, 21.77, 17.55.

4.4.8. Methyl 5-{2-(1*H*-benzo[*b*]azol-3-yl)ethylcarbamoyl}-2-hydroxy-5-(4-methylphenylsulfonyl)-1-cyclohexene-1-carboxylate. Viscous oil; IR ($CHCl_3$) 3452, 1652 cm^{-1}; ESI-MS: $C_{26}H_{29}N_2O_6S$ *m/z* (%)=497 (M^++1, 100); HRMS (EI, M^+) calcd for $C_{26}H_{28}N_2O_6S$ 496.1670, found 496.1678; ^1H NMR (300 MHz, $CDCl_3$): δ 12.08 (s, 1H), 8.25 (br s, 1H), 7.61 (d, *J*=7.5 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 1H), 7.25–7.11 (m, 4H), 7.04 (d, *J*=6.6 Hz, 1H), 6.78 (t, *J*=8.1 Hz, 1H), 3.66 (s, 3H), 3.63–3.55 (m, 2H), 3.02 (t, *J*=6.6 Hz, 2H), 2.90 (d, *J*=15.9 Hz, 1H), 2.78 (d, *J*=15.9 Hz, 1H), 2.37 (s, 3H), 2.36–2.28 (m, 3H), 2.15–2.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.63, 170.05, 164.98, 145.59, 136.42, 131.48, 129.69 (2×), 129.66 (2×), 126.92, 122.45, 122.09, 119.37, 118.50, 112.05, 111.34, 94.20, 70.12, 51.65, 40.48, 26.13, 25.23, 24.69, 24.53, 21.64.

4.4.9. [R_1=*t*-Bu, R_2=Tol]: Methyl 5-*t*-butylcarbamoyl-2-hydroxy-5-(4-methylphenylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=150–151°C; IR ($CHCl_3$) 3430, 3033, 1743, 1668 cm^{-1}; ESI-MS: $C_{20}H_{28}NO_6S$ *m/z* (%)=340 (100), 410 (M^++1, 5); HRMS (ESI, M^++1) calcd for $C_{20}H_{28}NO_6S$ 410.1638, found 410.1646; ^1H NMR (400 MHz, $CDCl_3$): δ 12.04 (s, 1H), 7.70 (dd, *J*=1.9, 8.1 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 2H), 6.55 (br s, 1H), 3.73 (s, 3H), 2.90 (d, *J*=15.6 Hz, 1H), 2.74 (d, *J*=15.6 Hz, 1H), 2.37 (s, 3H), 2.36–2.28 (m, 3H), 2.15–2.09 (m, 1H), 1.35 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.78, 170.01, 163.76, 145.77, 131.98, 130.00 (2×), 129.69 (2×), 94.50, 70.56, 51.71, 51.95, 28.32 (3×), 26.12, 25.23, 24.95, 21.70; Anal. calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65. Found: C, 58.78; H, 6.84.

4.4.10. [R_1=*t*-Bu, R_2=Ph]: Methyl 5-*t*-butylcarbamoyl-2-hydroxy-5-(4-phenylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=139–140°C; IR ($CHCl_3$) 3440, 3041, 1744, 1673 cm^{-1}; ESI-MS: $C_{19}H_{26}NO_6S$ *m/z* (%)=58 (78), 166 (49), 254 (78), 308 (75), 396 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{19}H_{26}NO_6S$ 396.1482, found 396.1482; ^1H NMR (400 MHz, $CDCl_3$): δ 12.04 (s, 1H), 7.84 (dd, *J*=1.9, 8.1 Hz, 2H), 7.69–7.65 (m, 1H), 7.56–7.52 (m, 2H), 6.53 (br s, 1H), 3.73 (s, 3H), 2.92 (dd, *J*=2.2, 15.6 Hz, 1H), 2.75 (d, *J*=15.6 Hz, 1H), 2.43–2.34 (m, 3H), 2.23–2.18 (m, 1H), 1.35 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.75, 170.00, 163.60, 135.06, 134.59, 130.08 (2×), 129.25 (2×), 94.43, 70.63, 51.99, 51.73, 28.40 (3×), 26.10, 25.34, 24.94; Anal. calcd for $C_{19}H_{25}NO_6S$: C, 57.70; H, 6.37. Found: C, 57.82; H, 6.52.

4.4.11. [R_1=*t*-Bu, R_2=Me]: Methyl 5-*t*-butylcarbamoyl-2-hydroxy-5-(4-methylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=141–142°C; IR ($CHCl_3$) 3436, 3031, 1738, 1667 cm^{-1}; ESI-MS: $C_{14}H_{24}NO_6S$ *m/z* (%)=58 (69), 149 (100), 246 (42), 334 (M^++1, 36); HRMS (ESI, M^++1) calcd for $C_{14}H_{24}NO_6S$ 334.1325, found 334.1324; ^1H NMR (400 MHz, $CDCl_3$): δ 12.07 (s, 1H), 6.33 (br s, 1H), 3.76 (s, 3H), 3.08 (dd, *J*=2.3, 15.6 Hz, 1H), 2.88 (s, 3H), 2.78 (dt, *J*=1.7, 15.6 Hz, 1H), 2.47–2.44 (m, 2H), 2.40–2.34 (m, 1H), 2.23–2.15 (m, 1H), 1.32 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.67, 169.92, 164.66, 94.14, 69.55, 52.18, 51.77, 36.66, 28.22 (3×), 25.87, 24.41, 23.66; Anal. calcd for $C_{14}H_{23}NO_6S$: C, 50.43; H, 6.95. Found: C, 50.37; H, 6.88.

4.4.12. [R_1=*t*-Bu, R_2=*n*-Bu]: Methyl 5-*t*-butylcarbamoyl-2-hydroxy-5-(4-*n*-butylsulfonyl)-1-cyclohexene-1-carboxylate. Mp=88–89°C; IR ($CHCl_3$) 3448, 3024, 1731, 1679 cm^{-1}; ESI-MS: $C_{17}H_{30}NO_6S$ *m/z* (%)=58 (45), 166

(63), 254 (92), 288 (90), 376 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{17}H_{30}NO_6S$ 376.1795, found 376.1791; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.02 (s, 1H), 6.38 (br s, 1H), 3.72 (s, 3H), 3.05 (dd, J=1.7, 15.6 Hz, 1H), 2.99–2.86 (m, 2H), 2.71 (d, J=15.6 Hz, 1H), 2.41–2.30 (m, 3H), 2.21–2.13 (m, 1H), 1.83–1.76 (m, 2H), 1.46–1.23 (m, 2H), 1.32 (br s, 9H), 0.89 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.70, 169.82, 164.75, 94.30, 69.48, 52.03, 51.69, 48.45, 28.20 (3×), 25.75, 24.55, 23.70, 22.47, 21.82, 13.45; Anal. calcd for $C_{17}H_{29}NO_6S$: C, 54.38; H, 7.78. Found: C, 54.57; H, 7.88.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for financial support.

References

1. For recent reviews, see: (a) Fruhauf, H. W. *Chem. Rev.* **1997**, *97*, 523–596. (b) Filippini, M. N.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27–76.
2. Ogura, K.; Yahata, N.; Minoguchi, M.; Ohtauki, K.; Takahashi, K.; Iida, H. *J. Org. Chem.* **1986**, *51*, 508–512.
3. (a) McLaughlin, M. J.; Shen, H. C.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609–613. (b) Zehnder, L. R.; Hsung, R. P.; Wang, J. S.; Golding, G. M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3876–3879. (c) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690–691. (d) Chang, M. Y.; Chang, B. R.; Tai, H. M.; Chang, N. C. *Tetrahedron Lett.* **2000**, *41*, 10273–10276. (e) Wei, L. L.; Hsung, R. P.; Sklenicka, H. K.; Gerasyuto, A. I. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1516–1518.
4. Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992; pp 88–99.
5. (a) Dawson, N.; Figg, W. D.; Brawley, O. W.; Bergan, R.; Cooper, M. R.; Reed, E.; Sartor, O. *Chin. Cancer Res.* **1998**, *4*, 37–44. (b) Waelbroeck, M.; Lazareno, S.; Plaff, O.; Friebe, T.; Tastoi, M.; Mutschler, E.; Lambert, G. *Br. J. Pharmacol.* **1996**, *119*, 1319–1330.
6. (a) Kiyota, H.; Shimizu, Y.; Oritani, T. *Tetrahedron Lett.* **2000**, *41*, 5887–5890. (b) Flaih, N.; Pham-Huy, C.; Galons, H. *Tetrahedron Lett.* **1999**, *40*, 3697–3698. (c) Zhu, J.; Pham-Huy, C.; Lemoine, P.; Tomas, A.; Galons, H. *Heterocycles* **1996**, *42*, 1923–1926. (d) Robin, S.; Zhu, J.; Galons, H.; Pham-Huy, C.; Claude, J. R.; Tomas, A.; Viossat, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1249–1252.
7. (a) Sandanayaka, V. P.; Zask, A.; Venkatesan, A. M.; Baker, J. *Tetrahedron Lett.* **2001**, *42*, 4605–4607. (b) Levin, J. I.; Venkatesan, A. M.; Chen, I. M.; Zask, A.; Sandanayaka, V. P. PCT Int. Appl. WO Patent 0,044,723, 2000. (c) Dack, K. N.; Whitlock, G. A. PCT Int. Appl. WO Patent 9,929,667, 1998. (d) Barta, T. E.; Becker, D. P.; Boehm, T. L.; De Crescenzo, G. A.; Villamil, C. I.; MzDonald, J. J.; Freskos, J. N.; Getman, D. P. PCT Int. Appl. WO Patent 9,925,687, 1999.
8. (a) Solomon, D. M.; Grace, M. J.; Fine, J. S.; Bober, L. A.; Sherlock, M. H. US patent 5,939,431, 1997. (b) Branca, Q.; Heitz, M. P.; Neidhart, W.; Stadler, H.; Vieira, E.; Wostl, W. US patent 5,393,875, 1995. (c) Maravetz, L. L.; Crawford, S. D.; Theodoridis, G. PCT Int. Appl. WO Patent 9,828,280, 1997.