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Importance of Sulfonylimidazolidinone Motif of 4-Phenyl-1-arylsulfonylimidazolidinones for Their Cytotoxicity: Synthesis of 2-Benzoyl-4-phenyl[1,2,5]thiazolidine-1,1-dioxides and Their Cytotoxcity

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For probing the importance of planarity of imidazolidinone motif of 4-phenyl-1-(benzenesulfonyl)imidazolidinones **1** for their cytotoxicity, 4-phenyl-2-(benzoyl)[1,2,5]thiadiazolidine-1,1-dioxide (**2a**), 4-phenyl-2-(*p*-toluoyl)[1,2,5]thiadiazolidine-1,1-dioxide (**2b**), 4-phenyl-2-(phenylcarbamoyl)[1,2,5]thiadiazolidine-1,1-dioxide (**3a**), and 4-phenyl-2-(*p*-tolylcarbamoyl)[1,2,5]thiadiazolidine-1,1-dioxide (**3b**) were prepared along with their regioisomers (**5a**, **5b**, **9a**, **9b**) and their cytotoxicity were measured against human lung carcinoma (A549), human colon carcinoma (COLO205), human ovarian cancer (SK-OV-3), human leukemic cancer (K562), and murine colon adenocarcinoma (Colon26) cell lines *in vitro*. All compounds prepared do not show any activity against all five cancer cell lines unlike **1**. Compounds **1** possess planarity of imidazolidinone, especially in sulfonylurea moiety (-SO_2NHCONH-). However compounds **2** and **3** have nonplanar 5-membered ring, [1,2,5]thiadiazolidine-1,1-dioxides. Such structural differentiation might result in the loss of activity. Therefore the inactivity of **2** and **3** could also be an indication for the necessity of planarity of imidazolidinone ring of **1** for their cytotoxic activity.

Key words: (Benzenesulfonyl)-4-Phenyl-1-imidazolidinones, Cytotoxicity, 2-(Benzoyl)-4-phenyl-[1,2,5]thiadiazolidine-1,1-dioxides

INTRODUCTION

Arylsulfonylimidazolidinones were reported (Jung, *et al.*, 1996; 1996; 1997; 1997; Hwang, *et al.*, 1999) as analogs possessing broad spectrum of potent activity against the various human cancer cell lines. Previous structure activity relationship study of **1** indicated that 4-phenyl-1-benzenesulfonyl midazolidinone (Jung and Kwak., 1997) is considered to be basic motif for their activity like N-phenyl-N'-benzenesulfonylurea in diarylsulfonylureas (Howbert, *et al.*, 1990). The necessity of imidazolidinone moiety for their cytotoxicity has been demonstrated using 4-phenyl-2-benzenesulfonamidooxazolines (Jung, *et al.*, 2001) and 2-(arylsulfonyl)-4-phenyl-[1,2,5]thiadiazolidine-1,1-dioxides (Kim and Jung, 2002). Although oxazoline derivatives has very similar conformation with imidazolidinones, these compounds has remarkably reduced activity. This indicates imidazolidinone ring has the important role in addition to conformational contribution. Presumably NH-CO unit participate hydrogen donor and acceptor with putative receptor as shown in x-ray crystallographic data (Park, *et al.*, 2000). Thiadiazolidine-1,1-dioxides deviate the planarity of imidazolidinone ring. This structural variation results in the complete loss of activity. To verify the importance of arylsulfonylurea structural unit (-SO_2NHCONH-) in 4-phenyl-1-benzenesulfonylimidazolidinone (**1**), acylated thiadiazolidine-1,1-dioxides (**2**, **3**) containing carbonylsulfamide unit (-CONHSO_2NH-) were prepared and their cytotoxicity were measured against their cytotoxicities were measured against human and murine cancer cell lines to compare against those of **1**.

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MATERIALS AND METHODS

Melting points (mp) were determined on Electrothermal 1A 9100 MK2 apparatus and are uncorrected. All com-

mercial chemicals were used as obtained and all solvents were purified by the standard procedures prior to use (Perrin and Armarego, 1982). Thin-layer chromatography was performed on E Merck silica gel GF-254 precoated plates and the identification was done with UV light and colorization with spray 10% phosphomolybdic acid followed by heating. Flash column chromatography was performed with E. Merck silica gel (230-400 mesh). IR spectra were recorded with Jasco IR-Report-100 IR spectrometer in cm^{-1} and corrected against peak at 1601 cm^{-1} of polystyrene. NMR spectra were measured against the peak of tetramethylsilane by Varian Unity Inova 400 NMR (400 MHz) spectrometers. Elemental analysis was performed with EA1110 elemental analyzer (CE Instrument).

Preparation of 2a, 5a, and 6a

Sodium hydride (60% in oil, 20 mg, 0.52 mmol) was dispersed in anhydrous tetrahydrofuran (25 mL) and (*S*)-(+)-4-phenyl-[1,2,5]thiadiazolidine-1,1-dioxide (**4**) (102 mg, 0.52 mmol) (Kim and Jung, 2002) was added under nitrogen flow. The resulting mixture was stirred for ten minutes and cooled to 0°C. Tetrahydrofuran solution (5 mL) of one equivalent of benzoyl chloride (73 mg, 0.52 mmol) was slowly added. The reaction mixture was stirred for two hours at 0°C and then additional six hours at room temperature. After addition of ethyl acetate (100 mL), the mixture was washed with 1% hydrochloric acid (50 mL) and water two times. The organic layer was dehydrated with anhydrous sodium sulfate and evaporated under vacuum to give the crude product, which was then separated by flash column chromatography.

(*S*)-(+)-4-phenyl-2-benzoyl[1,2,5]thiadiazolidine-1,1-dioxide (2a)

yield 17.0%; R_f 0.54 (hexane : ethyl acetate = 2 : 1); white solid; mp 159.6~161.0°C; $[\alpha]_D^{18}$ = 55.00 (c=0.4%, CH_3OH); IR (KBr) 3170, 1660, 1370, 1190 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.21 (dd, *J* = 10.8, 10.8 Hz, 1H), 4.47 (dd, *J* = 5.6, 10.8 Hz, 1H), 4.79 (d, *J* = 9.2 Hz, 1H), 5.00 (m, 1H), 7.43~7.61 (m, 8H), 7.83(d, *J* = 6.8 Hz, 2H); Anal. Calcd for $C_{15}H_{14}N_2O_3S$ C 59.59, H 4.67, N,9.27 Found: C 60.07, H 4.57, N 9.31.

(*S*)-(+)-3-phenyl-2-benzoyl[1,2,5]thiadiazolidine-1,1-dioxide (2b)

yield 17.0%; R_f 0.41 (hexane : ethyl acetate = 2 : 1); white solid; mp 188.0~188.7°C; $[\alpha]_D^{18}$ = 97.99 (c = 0.5%, CH_3OH); IR (KBr) 3240, 1650, 1370, 1190 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 3.47 (m, 1H), 4.03 (m, 1H), 5.71 (dd, *J* = 7.6, 9.2 Hz, 1H), 7.31~7.55 (m, 8H), 7.82 (m, 2H); Anal. Calcd for $C_{15}H_{14}N_2O_3S$ C 59.59, H 4.67, N 9.27 Found: C 60.65, H 4.96, N 9.03.

(*S*)-3-phenyl-2,5-dibenzoyl[1,2,5]thiadiazolidine-1,1-dioxide (6a)

yield 17.2%; R_f 0.71 (hexane : ethyl acetate = 2 : 1); white solid; mp 129.1~131.6°C; IR (KBr) 1690, 1670, 1380, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.97 (dd, *J* = 9.6, 12.8 Hz, 1H), 4.94 (dd, *J* = 7.6, 12.8 Hz, 1H), 5.78 (dd, *J* = 7.6, 9.6 Hz, 1H), 7.35~7.58 (m, 11H), 7.78~7.81 (m, 4H); Anal. Calcd for $C_{22}H_{18}N_2O_4S$ C 65.01, H 4.46, N 6.89 Found: C 65.78, H 4.45, N 6.81.

Preparation of 2b, 5b, and 6b

The same procedure used to prepare compounds **2a**, **5a**, and **6a** was employed to prepare compounds **2b**, **5b**, and **6b** using *p*-toluoyl chloride in place of benzoyl chloride.

(*S*)-4-phenyl-2-(*p*-toluoyl)[1,2,5]thiadiazolidine-1,1-dioxide (2b)

yield 31.6%; R_f 0.58 (hexane : ethyl acetate = 2 : 1); white solid; mp 151.9~152.5°C; IR (KBr) 3300, 1690, 1380, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.21 (dd, *J* = 10.8, 10.8 Hz, 1H), 4.48 (dd, *J* = 6.0, 10.8 Hz, 1H), 4.75 (s, 1H), 5.00 (m, 1H), 7.28~7.78 (m, 9H); Anal. Calcd for $C_{16}H_{16}N_2O_3S$ C 60.74, H 5.10, N 8.85 Found: C 61.98, H 5.42, N 8.46.

(*S*)-(+)-3-phenyl-2-(*p*-toluoyl)[1,2,5]thiadiazolidine-1,1-dioxide (5b)

yield 31.5%; R_f 0.44 (hexane : ethyl acetate = 2 : 1); white solid; mp 179.2~180.3°C; $[\alpha]_D^{18}$ = 81.99 (*c* = 0.5%, CH_3OH); IR (KBr) 3250, 1670, 1320, 1180 cm^{-1}; ^{1}H-NMR [$CDCl_3$ acetone-d_6(2 drops)] δ 2.40 (s, 3H), 3.50 (m, 1H), 3.95 (m, 1H), 5.70 (dd, *J* = 7.6, 8.8 Hz, 1H), 5.81 (dd, *J* = 7.2, 11.2 Hz, 1H), 7.30~7.51 (m, 7H), 7.76 (d, *J* = 7.8 Hz, 2H); Anal. Calcd for $C_{16}H_{16}N_2O_3S$ C 60.74, H 5.10, N 8.85 Found: C 62.41, H 5.52, N 8.41.

(*S*)-3-phenyl-2,5-di(*p*-toluoyl)[1,2,5]thiadiazolidine-1,1-dioxide (6b)

yield 12.4%; R_f 0.78 (hexane : ethyl acetate = 2 : 1); white solid; mp 169.5~171.2°C; IR (KBr) 1690, 1670, 1380, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.36 (s, 3H), 3.93 (dd, *J* = 9.6, 12.8 Hz, 1H), 4.91 (dd, *J* = 7.8, 12.8 Hz, 1H), 5.77 (dd, *J* = 7.8, 9.6 Hz, 1H), 7.187.23 (m, 4H), 7.357.57 (m, 5H), 7.69~7.73 (m, 4H); Anal. Calcd for $C_{24}H_{22}N_2O_4S$ C 66.34, H 5.10, N 6.45 Found: C 67.85, H 5.56, N 6.26.

Preparation of 3a and 9a

Sodium hydride (60% in oil, 20 mg, 0.52 mmol) was dispersed in anhydrous tetrahydrofuran (25 mL) and (S)-(+)-4-phenyl-[1,2,5]thiadiazolidine-1,1-dioxide (**4**) (102 mg, 0.52 mmol) (Kim and Jung, 2002) was added under nitrogen flow. The resulting mixture was stirred for ten minutes and cooled to 0°C. Tetrahydrofuran solution (5 mL) of phenyl isocyanate (62 mg, 0.52 mmol) was slowly added. The reaction mixture was stirred for two hours at 0°C. After addition of ethyl acetate (100 mL), the mixture was washed with

1% hydrochloric acid (50 mL) and water two times. The organic layer was dehydrated with anhydrous sodium sulfate and evaporated under vacuum to give the crude product, which was then separated by flash column chromatography.

(*S*)-(-)-4-phenyl-2-phenylcarbamoyl[1,2,5]thiadiazolidine-1,1-dioxide (3a)

yield 74.5%; R_f 0.52 (hexane : ethyl acetate = 2 : 1); white solid; mp 136.1~137.4; $[\alpha]_D^{18}$ = -2.99 (c = 1%, CH_3OH); IR (KBr) 3390, 3190, 1680, 1320, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.01 (dd, *J* = 8.8, 10.8 Hz, 1H), 4.47 (dd, *J* = 6.8, 10.8 Hz, 1H) 4.97 (m, 1H), 5.04 (d, *J* = 8.4 Hz, 1H), 7.14~7.44 (m, 9H) 7.74 (s, 1H); Anal. Calcd for $C_{15}H_{15}N_3O_3S$ C 56.77, H 4.76, N 13.24 Found: C 56.19, H 4.66, N 12.88.

(*S*)-4-phenyl-5-phenylcarbamoyl-[1,2,5]thiadiazolidine-1,1-dioxide (9a)

yield 14.9%; R_f 0.41 (hexane : ethyl acetate = 2 : 1); white solid; mp 167.4~168.5°C; IR (KBr) 3390, 3190, 1690, 1340, 1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.45 (m, 1H), 4.04 (m, 1H), 5.52 (dd, *J* = 5.6, 7.6 Hz, 1H), 6.89 (t, *J* = 7.8 Hz, 1H), 7.05~7.48 (m, 10H), 7.79 (s, 1H); Anal. Calcd for $C_{15}H_{15}N_3O_3S$ C 56.77, H 4.76, N 13.24 Found: C 57.52, H 4.91, N 12.85.

Preparation of 3b and 9b

The same procedure used to prepare compounds **3b** and **9b** was employed to prepare compounds **3b** and **9b** using *p*-tolyl isocyanate in place of phenyl isocyanate.

(*S*)-(-)-4-phenyl-2-(*p*-tolylcarbamoyl)[1,2,5]thiadiazolidine-1,1-dioxide (3b)

yield 31.6%; R_f 0.67 (hexane : ethyl acetate = 2 : 1); white solid; mp 122.7~124.1°C; $[\alpha]_D^{18}$ = -7.99 (c = 1%, CH_3OH); IR (KBr) 3390, 3220, 1700, 1350, 1190 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.98 (dd, *J* = 8.8, 10.8 Hz, 1H), 4.45 (dd, *J* = 7.2, 10.8 Hz, 1H), 4.94 (m, 1H), 5.08 (d, *J* = 7.2 Hz, 1H) 7.12~7.44 (m, 9H), 7.69 (s, 1H); Anal. Calcd for $C_{16}H_{17}N_3O_3S$ C 57.99, H 5.17, N 12.68 Found: C 57.44, H 5.04, N 12.17.

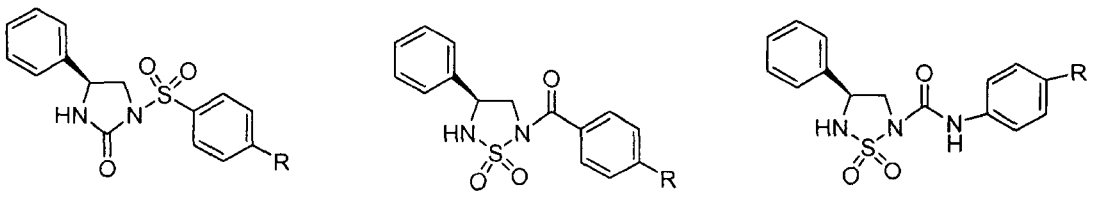
(*S*)-4-phenyl-5-(*p*-tolylcarbamoyl)[1,2,5]thiadiazolidine-1,1-dioxide (9b)

yield 21.6%; R_f 0.59 (hexane : ethylacetate = 2 : 1); white solid; mp 81.9~83.6°C; IR (KBr) 3390, 3220, 1690, 1320, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.40 (m, 1H), 4.00 (m, 1H), 5.00 (t, *J* = 8.8 Hz, 1H), 5.52 (dd, *J* = 4.0, 6.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H) 7.24~7.43 (m, 7H), 7.52 (s, 1H); Anal. Calcd for $C_{16}H_{17}N_3O_3S$ C 57.99, H 5.17, N 12.68 Found: C 57.35, H 5.13, N 11.89.

RESULTS AND DISCUSSION

To prepare compounds **2** and **3**, (*S*)-3-phenyl[1,2,5] thiadiazolidine-1,1-dioxides **4** (Kim and Jung, 2002) was treated with one equivalent of sodium hydride and then acylating agents (benzoyl chloride, -toluoyl chloride, phenyl isocyanate, or *p*-tolyl isocyanate) as shown in Fig. 2 and 4. The reaction results and select NMR data are summarized in Table I. In the reaction of **4** with benzoyl chloride (or *p*-toluoyl chloride), equal amount of **2** and their regioisomers **5** were formed along with dibenzoyl derivatives **6**. Meanwhile the treatment of **4** with isocyanate gave componds **3** and their regioisomers **7** without dicarbamoylated derivatives **10** in a ratio of about 4 : 1.

Structures of **2** and their regioisomers **5** was confirmed based on NMR spectra as shown in Table I. Compound **2a** exhibits the absorption peaks at 4.21 (dd) for proton Ha, 4.41 (dd) for proton Hb, and 5.00 (m) for proton Hc. Proton Hc is coupled with NH proton at 5-position as well as Ha and Hb. Thus it shows multiplet. These coupling patterns are also obvious in the spectra of **2b**. However the regioisomer **5a** and **5b** shows the multiplet peaks for Ha and Hb. Therefore aroyl of **2** are located at 2 position. These splitting patterns appears in the NMR spectra of **3** and **9**. Chemical shift changes for protons Ha, Hb, and Hc are another indication for the differentiation of regioisomers. Upon introduction of electron withdrawing group, benzoyl function, at 5-position of **4** to form **2**, chemical shifts for protons Ha and Hb are moved to downfield about 0.8 ppm for Ha and about 0.6 ppm for Hb. However chemical shift for Hc remains at nearly same position. These changes obviously result from the effect of electron withdrawing group located to the closest position. In the spectra of regioisomers



1a; R = H
1b: R = CH_3

2a; R = H
2b: R = CH_3

3a; R = H
3b: R = CH_3

Fig. 1. Design of (*S*)-2-benzoyl-4-phenyl-[1,2,5]thiadiazolidine-1,1-dioxides

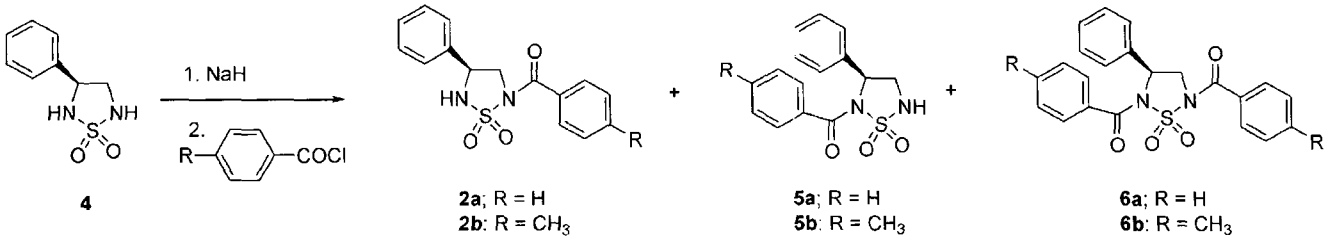
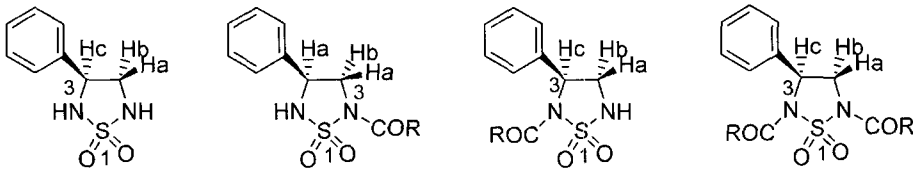


Fig. 2. Benzoylation of **4**

Table I. Summary of acylation of **4** and select NMR data



Compd No.	yield (%)	total yield (%)	Chemical shift (δ) and multiplicity[a]		
			Ha	Hb	Hc
4[b]			3.42(dd, *J* = 7.4, 11.4)	3.90(dd, *J* = 6.6, 11.4)	4.95(6.6, 7.4)
2a	17.0		4.21(dd, *J* = 10.8, 10.8)	4.47(dd, *J* = 5.6, 10.8)	5.00 (m)
5a	17.0	51.2	3.47(m)	4.03(m)	5.71 (dd, *J* = 7.6, 9.2)
6a	17.2		3.97(dd, *J* = 9.6, 12.8)	4.94(dd, *J* = 7.6, 12.8)	5.78(dd, *J* = 7.6, 9.6)
2b	31.6		4.21(dd, *J* = 10.8, 10.8)	4.48(dd, *J* = 6.0, 10.8)	5.00(m)
5b	31.5	75.5	3.50(m)	3.95(m)	5.70(dd, *J* = 7.6, 8.8)
6b	12.4		3.93(dd, *J* = 9.6, 12.8)	4.91(dd, *J* = 7.8, 12.8)	5.77(dd, *J* = 7.8, 9.6)
3a	74.0		4.01 (dd, *J* = 8.8, 10.8)	4.47(dd, *J* = 6.8, 10.8)	4.97(m)
9a	14.9	88.9	3.45(m)	4.04(m)	5.52(dd, *J* = 5.6, 7.6)
10a	0				
3b	70.5		3.98(dd, *J* = 8.8, 10.8)	4.45(dd, *J* = 7.2, 10.8)	4.94(m)
9b	21.6	92.1	3.40(m)	4.00(m)	5.52(dd, *J* = 4.0, 6.8)
10b	0				

[a]dd: doublet of doublet, m: multiplet, and J value is in Hz. [b]compound **4** (Kim and Jung, 2002)

5, absorption peaks for Ha and Hb slightly shift to downfield but peaks for Hc shift downfield about 0.75 ppm upon the introduction of benzoylation group at 2-position of **4**. Such trend also appears in the NMR spectra of **3** and **9**.

The different results of benzoylation and carbamoylation of **4** might be explained with the different acidity of NH proton of **2** and **3**. Fig. 3 outlines rational for formation of equal amount of **2** and their regioisomers **5**. Compound **4** was initially deprotonated and then benzoylated to form **2** and **5** inequal ratio presumably. Then unreacted deprotonated species of **4** abstracted proton from **2** and **5** due to increased acidity of NH proton after monobenzoylation and then benzoylation occurred to form a dibenzoylated compounds **6.** These compounds then acted as benzoylating agent to react with unreacted deprotonated species of **4**. In this final step, benzoylation reaction occurred between the less hindered side of **4** and the less hindered side of benzoyl group of **6**. This final reaction ensure the formation of equal amount of **2** and **5** and variable amount of **6**. Meanwhile monocarbamoylation of **4** less increases the acidity of NH proton compared to benzoylation. Therefore only monocarbamoylation occurred more from the less hindered side of **4** to give major product **3** and minor product 9 without formation of dicarbamoylated compounds **10**.

Cytotoxicities of **2**, **3**, **5**, **6**, and **9** were measured three times against measured against human lung carcinoma (A549), human colon carcinoma (COLO205), human ovarian cancer (SK-OV-3), human leukemic cancer (K562), and murine colon adenocarcinoma (Colon26) cell lines *in vitro*

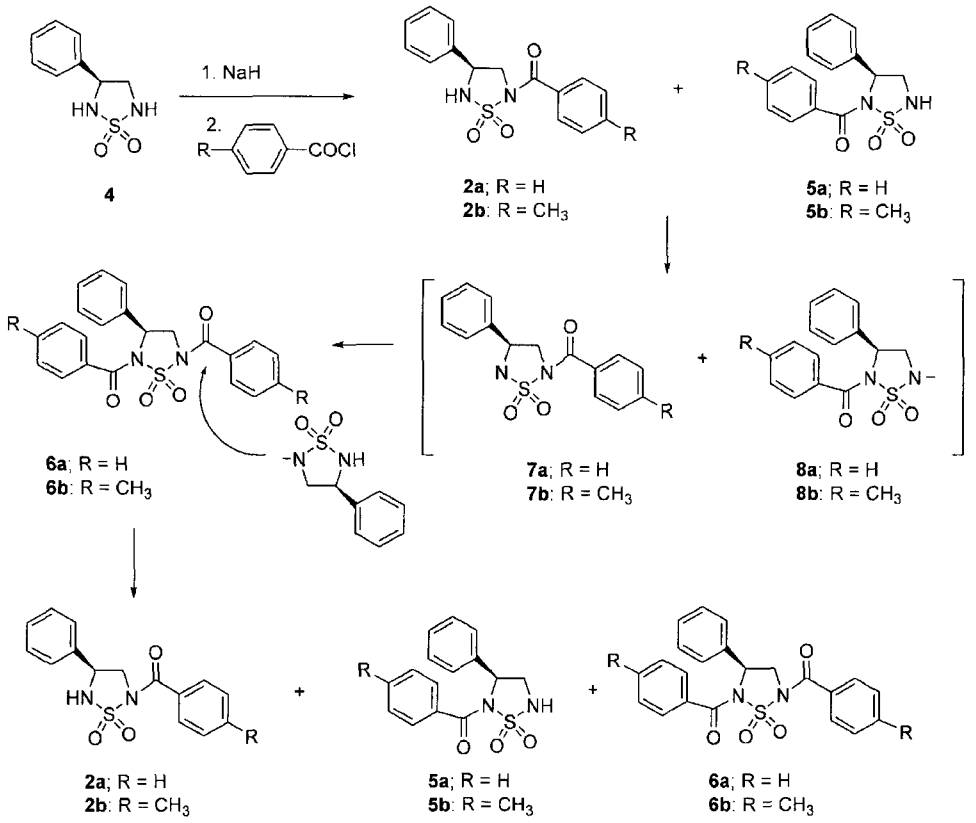


Fig. 3. Mechanism for benzoylation of **4**

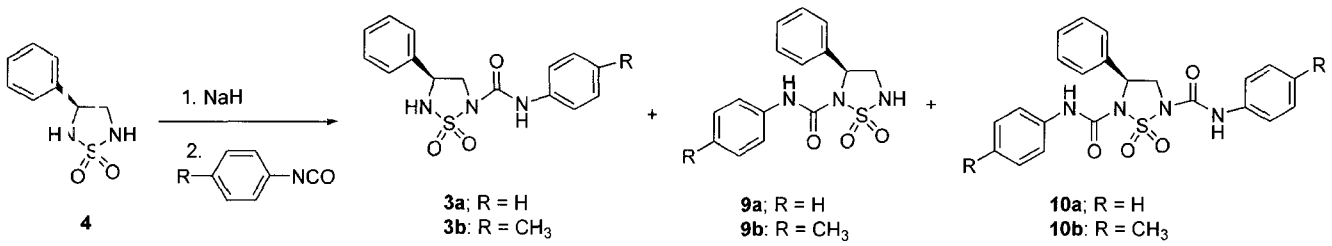


Fig. 4. Carbamoylation of **4**

Table II. Cytotoxicity of compounds **2**, **3**, **5**, **6**, and **9**

Compound No.	R	IC_{50} (μg/ml)[a]				
		A549	Colo205	K562	SK-OV-3	Colon26
2a	-H	>25	>25	>25	>25	>25
5a		>25	>25	>25	>25	>25
6a		>25	>25	>25	>25	>25
2b	-CH_3	>25	>25	>25	>25	>25
5b		>25	>25	>25	>25	>25
6b		>25	>25	>25	>25	>25
3a	-H	>25	>25	>25	>25	>25
9a		>25	>25	>25	>25	>25
3b	-CH_3	>25	>25	>25	>25	>25
9b		>25	>25	>25	>25	>25
doxorubicin		0.671	0.419	0.158	0.796	0.222

using MTT assay (Everitt *et al.*, 1987, Skehon *et al.*, 1990). The results from these tests are shown as mean IC_{50} values in Table II. Compounds **2**, **3**, **5**, **6**, and **9** do not show any activity against all five cancer cell lines. Although the inactivities of compounds **5**, **6**, and **9** are expected when considering structure activity relationship of **1** (regioisomer of **1** and large substituent at 3 position of **1** shows very weak or no activity), the complete disappearance of activity of **2** and **3** are rather unexpected. Because the overall conformation of **2** and **3** are very similar to that of **1**. Compounds **1** possess planarity of imidazolidinone, especially in sulfonylurea moiety (-$SO_2NHCONH$-). However compounds **2** and **3** have nonplanar 5-membered ring, [1,2,5] thiadiazolidine-1,1-dioxides. Such structural differentiation might result in the loss of activity. This feature had been demonstrated with inactivity of 4-phenyl-2-(arylsulfonyl)[1,2,5]

thiadiazolidine-1,1-dioxides (Kim and Jung, 2002). Therefore, the inactivity of **2** and **3** could also be another indication for the necessity of planarity of imidazolidinone ring of **1** for their cytotoxic activity.

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