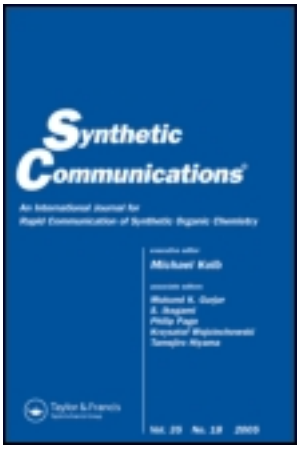

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Regioselective Alkylation of Thiazolylsulfonamides: Direct and Efficient Synthesis of 3-Alkylthiazolidene Derivatives

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Abstract: Various *N*-3-alkylated thiazolidenesulfonamide derivatives were efficiently prepared by the direct *endo*-selective alkylation of thiazolylsulfonamides. The effects of different bases and solvents were investigated, and the NaH–THF combination was found to be the most effective at conferring high yields and *endo*-selectivity.

Keywords: Alkylation, alkyl halide, regioselective, sulfonamide

Thiazolylbenzenesulfonamide analogues show great potential as novel anti–human immunodeficiency virus (HIV) agents.[1] The pharmacological profiles of these chemicals are critically dependent on the nature of the substituents on the thiazole and phenyl rings: an *endo*-alkylated compound (**1a**) shows more potent antiretroviral activity than an *exo*-alkylated compound (**1b**) (Fig. 1). However, further exploration of their structure–activity relationship requires the identification of a convenient approach to *N*-3-alkylated thiazolidene synthesis.

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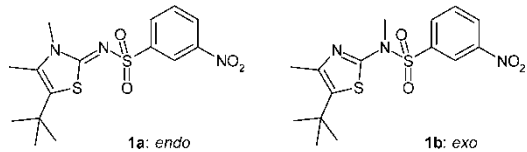
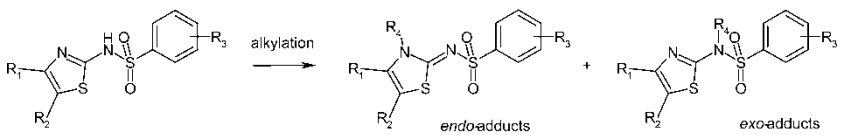


Figure 1. Structure of thiazolylsulfonamide derivatives.

The synthesis of *N*-3-alkylated thiazolidenesulfonamides has been reported through the cyclization of α-bromoketones and *N*-alkyl-*N*′-benzenesulfonylthioureas or by ring opening on 5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles.[2,3] However, the starting materials for these reactions need to be prepared in many steps. Although several methods have been suggested for achieving this objective (for example, through the sulfonylation of *N*-3-alkylated aminothiazoles), the yields are low and it is difficult to synthesize a variety of substituents.[4] Kaye and colleagues reported the *N*-3 alkylation of 2-acetamidothiazole using $LiNH_2$ as a base;[5] however, the reaction was limited to the amide and the yield was low. These difficulties prompted us to explore a direct synthesis to obtain the desired *endo*-alkylated thiazolidenesulfonamides in good yield in the presence of various substituents. Here we describe the efficient *endo*-selective alkylation of thiazoles, which allows the direct introduction of various alkyl groups at the 3-position of thiazoles (Scheme 1).

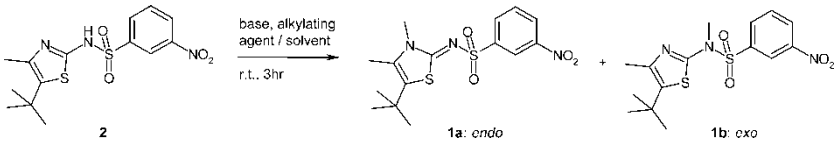
Initially, the effects of several bases and solvents on the selectivity of *N*-3 methylation were investigated (Table 1). The alkylated positions of the products were confirmed by their nuclear magnetic resonance (NMR) spectra. Nuclear Overhauser effects (NOE) between the alkyl proton substituted on the nitrogen and either the 4-methyl or aromatic proton were observed in the *endo*- or *exo*-adduct, respectively (Fig. 2). When trimethylsilyldiazomethane was used as a methylating agent, alkylation proceeded non-selectively (Run 1). In the absence of a base, alkylation with iodomethane did not occur (Run 2). Using Hünig's base, which has been reported to be effective for the *endo*-alkylation of 2-aminopyridines,[6] the reaction proceeded to give the *endo*-adduct with moderate selectivity in low yield (Run 3).

To improve the selectivity and yield, further investigation of the bases was carried out using THF as a solvent. The use of K_2CO_3, Cs_2CO_3, and NaOH gave improved yields (Runs 4–6). Alkylation with strong bases,



Scheme 1.

Table 1. The effect of bases and solvents on methylation



Run	Base	Alkylating agents	Solvent	Selectivity[a] *endo* (**1a**)	Selectivity[a] *exo* (**1b**)	Yield[b] (%)
1	None	$TMSCHN_2$	MeOH	59	41	30
2	None	MeI	THF	—	—	N.R.[c]
3	DIPEA[d]	MeI	THF	81	19	23
4	K_2CO_3	MeI	THF	80	20	70
5	Cs_2CO_3	MeI	THF	78	22	71
6	NaOH	MeI	THF	82	18	79
7	*t*-BuOK	MeI	THF	95	5	45
8	NaHMDS[e]	MeI	THF	95	5	50
9	NaH	MeI	THF	>98	<2	92
10	NaH	MeI	DMF	97	3	63
11	NaH	MeI	1,4-dioxane	97	3	38
12	NaH	MeI	DMSO	97	3	39

[a]The *endo* and *exo* selectivity were determined by high-performance liquid chromatography (HPLC) area (%).
[b]Isolated yield of *endo*-adduct **1a**.
[c]N.R.: no reaction.
[d]DIPEA: *N,N*-diisopropylethylamine.
[e]NaHMDS: sodium hexamethyldisilazide.

such as *t*-BuOK and NaHMDS, proceeded with high selectivity, but the yields were low and by-products were observed (Runs 7 and 8). It should be noted that the use of NaH significantly enhanced both the *endo*-selectivity and the yield (Run 9). Although solvent effects on the regioselectivity of alkylation were not apparent, the use of DMF, DMSO, and 1,4-dioxane decreased the product yields and the starting materials persisted (Runs 10–12). The regioselectivity of methylation was found to be dependent on the strength

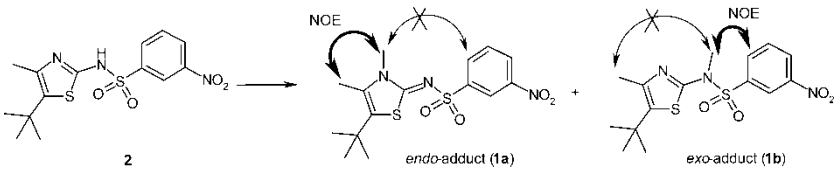


Figure 2. Key NOE correlations of *endo*- and *exo*-adducts.

of the base used. These results suggest that the alkylation position might be kinetically controlled and the derived anion might be favored to afford *endo*-products because of steric repulsion of the benzenesulfonyl group. For regioselective *N*-3-alkylation, the optimal combination was found to be NaH–THF.

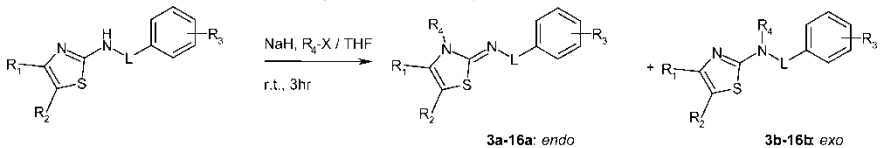
We next explored the scope and limitations of various alkylating agents and thiazoles using the NaH–THF combination (Table 2). In the case of bulky alkylating agents, such as iodoethane, benzylbromide, ethyl bromoacetate, and 1,3-dioxorane-2-ylethylbromide, *endo*-adducts were obtained in moderate yields with high selectivity (Runs 1–4). The alkylation proceeded efficiently without decomposition with ester or acetal substituents (Runs 3 and 4). The effects of substituents on the thiazole and phenyl rings were also investigated (Runs 5–12). The position and the electronic nature of the substituent (R_3) on the phenyl ring had little effect on the selectivity of the alkylation; however, the selectivity was highly dependent on the nature of the substituent (R_1) at the 4-position of the thiazole ring. The introduction of electron-withdrawing substituents at the 4-position led to a decrease in *endo*-selectivity (Runs 6 and 7). These results suggested that the decrease of *endo*-selectivity was due to reducing the nucleophilicity or increasing the steric bulkiness of the ring nitrogen through electron-withdrawing substituents. When alkylating amido- and ureido-thiazole, *endo*-methyl compounds were obtained in high yields (Runs 13 and 14). These results demonstrate that NaH–THF is effective for the synthesis of various *N*-3-alkylated thiazolidene derivatives.

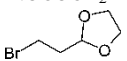
In conclusion, direct regioselective alkylation of thiazolylsulfonamides at the *N*-3 position was achieved using NaH–THF. We also explored the scope and limitations of this reaction and revealed the effects of thiazole and phenyl-ring substituents. This method allows the convenient and efficient preparation of various *N*-3-alkylated thiazolidene derivatives. In addition, it enables the detailed exploration of thiazolidene analogues as a novel class of anti-HIV agents.

GENERAL PROCEDURE

Melting points were determined on a Yanaco micromelting apparatus or Büchi melting-point apparatus B-545 and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) using a JEOL JNM-EX400, JNM-GX500, or JNM-A500 spectrometer. Chemical shifts are recorded in parts per million (δ), downfield relative to tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on a JEOL JMS-DX300 or a Hitachi M-80 mass spectrometer. Elemental analysis was carried out on Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC7000S ion chromatoanalyzer. Chromatographic separations were performed using a silica-gel column

Table 2. The effect of substituents on the regioselective alkylation



Run	L	R_1	R_2	R_3	R_4-X	Selectivity[a] *endo*	Selectivity[a] *exo*	Yield[b] (%)
1	SO_2	Me	*t*-Bu	3-NO_2	EtI	85 (**3a**)	15 (**3b**)	70
2	SO_2	Me	*t*-Bu	3-NO_2	BnBr	85 (**4a**)	15 (**4b**)	75
3	SO_2	Me	*t*-Bu	3-NO_2	$EtOCOCH_2Br$	>98 (**5a**)	<2 (**5b**)	92
4	SO_2	Me	*t*-Bu	3-NO_2		>98 (**6a**)	<2 (**6b**)	75
5	SO_2	H	*i*-Pr	3-NO_2	MeI	>98 (**7a**)	<2 (**7b**)	76
6	SO_2	CO_2Me	*i*-Pr	3-NO_2	MeI	63 (**8a**)	37 (**8b**)	43
7	SO_2	CF_3	*i*-Pr	3-NO_2	MeI	27 (**9a**)	73 (**9b**)	19
8	SO_2	Me	*t*-Bu	H	MeI	>98 (**10a**)	<2 (**10b**)	95
9	SO_2	Me	*t*-Bu	2-NO_2	MeI	82 (**11a**)	18 (**11b**)	62
10	SO_2	Me	*t*-Bu	4-NO_2	MeI	95 (**12a**)	5 (**12b**)	50
11	SO_2	Me	*t*-Bu	3-OMe	MeI	83 (**13a**)	17 (**13b**)	76
12	SO_2	Me	*t*-Bu	3-Cl	MeI	95 (**14a**)	5 (**14b**)	90
13	CO	Me	*t*-Bu	3-NO_2	MeI	81 (**15a**)	19 (**15b**)	71
14	CONH	Me	*t*-Bu	3-NO_2	MeI	86 (**16a**)	14 (**16b**)	60[c]

[a]See footnotes to Table 1.
[b]*Isolated yield of endo*-adducts **3a–16a**.
[c]Anilino-nitrogen was also alkylated.

(Merck Kieselgel 60). HPLC was performed using Hitachi Degasser L-7610 under these conditions: column: Wakosil-II 5C18 AR, dimensions: 4.6 × 30 mm, mobile phase: 5 mM of trifluoroacetic acid (TFA) in methanol/5 mM TFA in $H_2O = 10:90$, flow late: 4.0 mL/min, temperature: 35°C, detection: UV at 254 nm. The following known 2-aminothiazoles were prepared as described in the literature.[4,7,8] The *exo*-adducts **5b**, **7b**, **8b**, and **11b–14b** were not isolated and the structure were assumed by HPLC data.

General Procedure for the Sulfonylation of 2-Aminothaizoles

Sulfonylchloride (12 mmol) was added to a solution of 2-aminothiazole (10 mmol) in pyridine (50 ml) and the solution was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, 1 M of hydrochloric acid, and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography (ethyl acetate–hexane) to give target *N*-thiazolylbenzensulfonamide.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-nitrobenzenesulfonamide (2):** 69% yield; mp 212–213°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.30 (9H, s), 2.16 (3H, s), 7.86 (1H, t, $J = 8.3$ Hz), 8.21 (1H, dd, $J = 2.0$, 8.3 Hz), 8.42 (1H, ddd, $J = 1.8$, 2.0, 8.3 Hz), 8.46 (1H, t, $J = 1.8$ Hz), 12.58 (1H, br s). FAB-MS m/z: 356 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{17}N_3O_4S_2$: C, 47.31; H, 4.82; N, 11.82; S, 18.04. Found: C, 47.06; H, 4.84; N, 11.80; S, 17.84.

***N*-(5-Isopropyl-1,3-thiazol-2-yl)-3-nitrobenzenesulfonamide:** 51% yield; mp 162–163°C (toluene). ^{1}H NMR (DMSO-d_6) δ: 1.19 (6H, d, $J = 6.8$ Hz), 2.94 (1H, heptet, $J = 6.8$ Hz),7.05 (1H, s), 7.86 (1H, dd, $J = 7.8$, 8.3 Hz), 8.23 (1H, br d, $J = 7.8$ Hz), 8.42 (1H, ddd, $J = 1.5$, 1.9, 8.3 Hz), 8.47 (1H, dd, $J = 1.5$, 1.9 Hz), 12.71 (1H, br s). FAB-MS m/z: 328 ($M^+ + 1$). Anal. calcd. for $C_{12}H_{13}N_3O_4S_2$: C, 44.02; H, 4.00; N, 12.84; S, 19.59. Found: C, 43.96; H, 3.93; N, 12.78; S, 19.63.

Methyl 5-isopropyl-2-{[(3-nitrophenyl)sulfonyl]amino}-1,3-thiazole-4-carboxylate: 75% yield; mp 131–132°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.30 (6H, d, $J = 7.0$ Hz), 3.95 (1H, heptet, $J = 7.0$ Hz), 3.93 (3H, s), 7.69 (1H, dt, $J = 7.7$, 8.3 Hz), 8.27 (1H, ddd, $J = 1.1$, 1.8, 7.7 Hz), 8.38 (1H, ddd, $J = 1.1$, 2.4, 8.3 Hz), 8.77 (1H, t, $J = 1.8$ Hz). FAB-MS m/z: 386 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{15}N_3O_6S_2$: C, 43.63; H, 3.92; N, 10.90; S, 16.64. Found: C, 43.50; H, 4.00; N, 10.75; S, 16.44.

***N*-(5-Isopropyl-4-trifluoromethyl-1,3-thiazol-2-yl)-3-nitrobenzenesulfonamide:** 78% yield; mp 257–259°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.14 (6H, d, $J = 6.0$ Hz), 3.24 (1H, m), 7.71 (1H, dt, $J = 1.1$, 7.1 Hz), 8.13 (1H, dd, $J = 1.1$, 7.1 Hz), 8.26 (1H, dd, $J = 1.1$, 7.1 Hz), 8.49

(1H, d, $J = 1.8$ Hz). FAB-MS m/z: 393 ($M^+ - 1$). Anal. calcd. for $C_{13}H_{12}F_3N_3O_4S_2$: C, 39.49; H, 3.06; N, 10.63; S, 16.22; F, 14.42. Found: C, 39.52; H, 3.01; N, 10.74; S, 16.21; F, 14.19.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide:** 61% yield; mp 224–225°C (ethyl acetate–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.28 (9H, s), 2.14 (3H, s), 7.54 (3H, m), 7.78 (2H, m), 12.32 (1H, br s). FAB-MS m/z: 311 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{18}N_2O_2S_2$: C, 54.17; H, 5.84; N, 9.02; S, 20.66. Found: C, 54.05; H, 5.94; N, 8.95; S, 20.52.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-2-nitrobenzenesulfonamide:** 79% yield; ^{1}H NMR (DMSO-d_6) δ: 1.30 (9H, s), 2.18 (3H, s), 7.80 (2H, m), 7.87 (1H, m), 8.03 (1H, m), 12.65 (1H, br s). FAB-MS m/z: 356 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{17}N_3O_4S_2$: C, 47.31; H, 4.82; N, 11.82; S, 18.04. Found: C, 47.51; H, 4.67; N, 12.00; S, 17.83.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-4-nitrobenzenesulfonamide:** 85% yield; mp 206–207°C (ethyl acetate–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.30 (9H, s), 2.16 (3H, s), 8.03 (2H, d, $J = 8.8$ Hz), 8.36 (2H, d, $J = 8.8$ Hz), 12.58 (1H, br s). FAB-MS m/z: 356 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{17}N_3O_4S_2 \cdot 0.2H_2O$: C, 46.83; H, 4.88; N, 11.70; S, 17.86. Found: C, 46.87; H, 4.85; N, 11.71; S, 17.76.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-chlorobenzenesulfonamide:** 99% yield; mp 182–183°C (acetonitrile). ^{1}H NMR (DMSO-d_6) δ: 1.29 (9H, s), 2.16 (3H, s), 7.58 (1H, t, $J = 7.8$ Hz), 7.67 (1H, br d, $J = 7.8$ Hz), 7.74 (1H, br s), 7.75 (1H, br d, $J = 7.8$ Hz), 12.46 (1H, br s). FAB-MS m/z: 345 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{17}ClN_2O_2S_2$: C, 48.76; H, 4.97; N, 8.12; S, 18.60; Cl, 10.28. Found: C, 48.53; H, 4.87; N, 8.09; S, 18.88; Cl, 10.33.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-methoxybenzenesulfonamide:** 61% yield; mp 205–207°C (ethyl acetate). ^{1}H NMR (DMSO-d_6) δ: 1.29 (9H, s), 1.98 (3H, s), 3.80 (3H, s), 7.14 (1H, dd, $J = 2.5$, 8.3 Hz), 7.26 (1H, t, $J = 2.5$ Hz), 7.36 (1H, br d, $J = 7.8$ Hz), 7.45 (1H, t, $J = 7.8$ Hz), 12.34 (1H, br s). FAB-MS m/z: 341 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{2/}N_2O_3S_2$: C, 52.92; H, 5.92; N, 8.23; S, 18.84. Found: C, 53.11; H, 5.93, N; 8.15, S; 18.87.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-nitrobenzamide:** prepared with 3-nitrobenzoyl chloride in the same manner. 81% yield; mp 173–175°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.43 (3H, s), 7.74 (1H, m), 8.45 (3H, m), 9.03 (1H, br s). FAB-MS m/z: 320 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16; S, 10.04. Found: C, 56.27; H, 5.07; N, 13.28; S, 9.96.

***N*-(5-*tert*-butyl-4-methyl-1,3-thiazol-2-yl)-*N*′-(3-nitrophenyl)urea:** prepared with 3-nitrobenzoyl isocyanate in the same manner. 98% yield; mp 203–205°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.36 (9H, s), 2.28 (3H, s), 7.55 (1H, t, $J = 8.3$ Hz), 7.81 (2H, m), 8.61 (1H, t, $J =$ 2.0 Hz), 9.43 (1H, br s). FAB-MS m/z: 335 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{18}N_4O_3S$: C, 53.88; H, 5.43; N, 16.75; S, 9.59. Found: C, 53.80; H, 5.38; N, 16.68; S, 9.50.

General Procedure for the Alkylation of *N*-Thiazolylbenzensulfonamide

To a solution of *N*-thiazolylbenzensulfonamide (5.0 mmol) in tetrahydrofuran (15 ml) was added sodium hydride (60% dispersion in mineral oil: 6.0 mmol) and iodomethane (15 mmol) under ice-bath cooling. The solution was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica-gel column chromatography (ethyl acetate–hexane) to give the target 3-alkylated thiazolidene derivatives.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-nitrobenzenesulfonamide (1a):** mp 143–145°C. ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s), 2.12 (3H), 3.60 (3H, s), 7.84 (1H, dd, $J = 7.9$, 8.3 Hz), 8.26 (1H, br d, $J = 7.9$ Hz), 8.41 (1H, dd, $J = 2.5$, 8.3 Hz), 8.49 (1H, t, $J = 2.5$ Hz). FAB-MS m/z: 370 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{19}N_3O_4S_2$: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.69; H, 5.25; N, 11.31; S, 17.37.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-*N*-methyl-3-nitrobenzenesulfonamide (1b):** mp 91–92°C. ^{1}H NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.26 (3H), 3.30 (3H, s), 7.72 (1H, t, $J = 7.8$ Hz), 8.25 (1H, br d, $J = 7.8$ Hz), 8.48 (1H, t, $J = 1.9$ Hz), 8.57 (1H, ddd, $J = 0.9$, 1.9, 8.3 Hz). FAB-MS m/z: 370 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{19}N_3O_4S_2$: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.87; H, 5.28; N, 11.27; S, 17.30.

***N*-(5-*tert*-Butyl-3-ethyl-4-methyl-1,3-thiazol-2(3*H*)-ylidene)-3-nitrobenzenesulfonamide (3a):** mp 139–141°C (diethyl ether–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.12 (3H, t, $J = 6.8$ Hz), 1.32 (9H, s), 2.31 (3H, s), 3.96 (2H, q, $J = 6.8$ Hz), 7.85 (1H, t, $J = 8.3$ Hz), 8.25 (1H, ddd, $J = 1.0$, 1.9, 8.3 Hz), 8.42 (1H, dd, $J = 1.0$, 1.9, 8.3 Hz), 8.48 (1H, t, $J = 1.9$ Hz). FAB-MS m/z: 384 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{21}N_3O_4S_2$: C, 50.11; H, 5.52; N, 10.96; S, 16.72. Found: C, 50.06; H, 5.49; N, 11.02; S, 16.81.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-*N*-ethyl-3-nitrobenzenesulfonamide (3b):** mp 105–107°C (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, $J = 7.0$ Hz), 1.41 (9H, s), 2.34 (3H, s), 3.83 (2H, d, $J = 7.0$ Hz), 7.72 (1H, t, $J = 8.2$ Hz), 8.17 (1H, ddd, $J = 0.9$, 1.6, 7.7 Hz), 8.44 (1H, ddd, $J = 0.9$, 2.2, 8.2 Hz), 8.72 (1H, t, $J = 1.8$ Hz). FAB-MS m/z: 384 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{21}N_3O_4S_2$: C, 50.11; H, 5.52; N, 10.96; S, 16.72. Found: C, 50.17; H, 5.55; N, 10.96; S, 16.71.

***N*-(3-Benzyl-5-*tert*-butyl-4-methyl-1,3-thiazol-2(3*H*)-ylidene)-3-nitrobenzenesulfonamide (4a):** mp 213–214°C. ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 2.20 (3H, s), 5.21 (2H, s), 6.96 (4H, m), 7.22 (2H, m), 7.58 (1H, t, $J = 7.8$ Hz), 8.15 (2H, m), 8.30 (1H, ddd, $J = 1.0$, 2.5, 8.3 Hz), 8.68 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 446 ($M^+ + 1$). Anal. calcd. for $C_{21}H_{23}N_3O_4S_2$: C, 56.61; H, 5.20; N, 9.43; S, 14.39. Found: C, 56.56; H, 5.25; N, 9.45; S, 14.50.

***N*-Benzyl-*N*-(5-*tert*-butyl-4-methyl-1,3-thiazol-2-yl)-3-nitrobenzenesulfonamide (4b):** mp 142–143°C. ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 2.33 (3H, s), 5.02 (2H, s), 7.24 (4H, m), 7.35 (2H, m), 7.64 (1H, t, $J = 7.8$ Hz), 8.04 (1H, m), 8.38 (1H, ddd, $J = 1.0, 2.5, 8.3$ Hz), 8.58 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 446 ($M^+ + 1$). Anal. calcd. for $C_{21}H_{23}N_3O_4S_2$: C, 56.61; H, 5.20; N, 9.43; S, 14.39. Found: C, 56.65; H, 5.19; N, 9.39; S, 14.28.

Ethyl [5-*tert*-butyl-4-methyl-2-{[(3-nitrophenyl)sulfonyl]imino}-1,3-thiazol-3(2*H*)-yl]acetate (5a): mp 104–105°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.24 (3H, t, $J = 7.0$ Hz), 1.37 (9H, s), 2.21 (3H, s), 4.17 (2H, q, $J = 7.0$ Hz), 4.71 (2H, s), 7.64 (1H, t, $J = 7.9$ Hz), 8.28 (2H, m), 7.73 (1H, t, $J = 1.8$ Hz). FAB-MS m/z: 442 ($M^+ + 1$). Anal. calcd. for $C_{18}H_{23}N_3O_6S_2$: C, 48.97; H, 5.25; N, 9.52; S, 14.53. Found: C, 48.99; H, 5.20; N, 9.47; S, 14.49.

***N*-[5-*tert*-Butyl-3-[2-(1,3-dioxolan-2-yl)ethyl]-4-methyl-1,3-thiazol-2(3*H*)-ylidene]-3-nitrobenzenesulfonamide (6a):** mp 212–214°C (ethyl acetate–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s), 1.85 (2H, m), 2.29 (3H, s), 3.71 (2H, m), 3.84 (2H, m), 4.00 (2H, m), 4.81 (1H, t, $J = 4.4$ Hz), 7.85 (1H, t, $J = 7.8$ Hz), 8.25 (1H, m), 8.41 (1H, br d, $J = 2.4$, 8.3 Hz), 8.49 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 456 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{25}N_3O_6S_2$: C, 50.09; H, 5.53; N, 9.22; S, 14.08. Found: C, 50.00; H, 5.64; N, 9.02; S, 13.98.

***N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-*N*-[2-(1,3-dioxolan-2-yl)-ethyl]-3-nitrobenzenesulfonamide (6b):** mp 185–187°C (ethyl acetate–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.38 (9H, s), 1.86 (2H, m), 2.29 (3H, s), 3.74 (2H, m), 3.85 (4H, m), 4.82 (1H, t, $J = 4.9$ Hz), 7.95 (1H, t, $J = 8.3$ Hz), 8.26 (1H, br d, $J = 7.8$ Hz), 8.49 (1H, t, 2.0 Hz), 8.56 (1H, dd, $J = 1.5$, 8.3 Hz). FAB-MS m/z: 456 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{25}N_3O_6S_2$: C, 50.09; H, 5.53; N, 9.22; S, 14.08. Found: C, 49.95; H, 5.60; N, 8.99; S, 13.85.

***N*-(5-Isopropyl-3-methyl-1,3-thiazol-2(3*H*)-ylidene)-3-nitrobenzenesulfonamide (7a):** mp 150–151°C (isopropanol). ^{1}H NMR (DMSO-d_6) δ: 1.19 (6H, d, $J = 6.9$ Hz), 2.95 (1H, heptet, $J = 6.9$ Hz), 3.45 (3H, s), 7.22 (1H, s), 7.86 (1H, d, $J = 7.8$, 8.3 Hz), 8.26 (1H, br d, $J = 7.8$ Hz), 8.43 (1H, ddd, $J = 1.0$, 1.9, 8.3 Hz), 8.49 (1H, t, $J = 1.9$ Hz). FAB-MS m/z: 342 ($M^+ + 1$). Anal. calcd. for $C_{13}H_{15}N_3O_4S_2$: C, 45.73; H, 4.43; N, 12.31; S, 18.78. Found: C, 45.66; H, 4.31; N, 12.30; S, 18.89.

Methyl 5-Isopropyl-3-methyl-2-{[(3-nitrophenyl)sulfonyl]imino}-2,3-dihydro-1,3-thiazole-4-carboxylate (8a): mp 120–121°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.29 (6H, d, $J = 6.8$ Hz), 3.67 (3H, s), 3.68 (1H, heptet, $J = 6.8$ Hz), 3.93 (3H, s), 7.88 (1H, br t, $J = 8.2$ Hz), 8.29 (1H, br d, $J = 7.7$ Hz), 8.37 (1H, dd, $J = 2.0$, 8.2 Hz), 8.79 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 400 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{17}N_3O_6S_2$: C, 45.10; H, 4.29; N, 10.52; S, 16.06. Found: C, 44.93; H, 4.10; N, 10.62; S, 16.09.

Methyl 5-*tert*-butyl-2-{methyl[(3-nitrophenyl)sulfonyl]amino}-1,3-thiazole-4-carboxylate (8b): mp 121–123°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.36 (6H, d, $J = 6.9$ Hz), 3.48 (3H, s), 3.89 (3H, s), 4.07

(1H, heptet, $J = 6.9$ Hz), 7.75 (1H, t, $J = 8.1$ Hz), 8.14 (1H, m), 8.48 (1H, ddd, $J = 1.0$, 2.0, 8.1 Hz), 8.69 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 400 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{17}N_3O_6S_2$: C, 45.10; H, 4.29; N, 10.52; S, 16.06. Found: C, 44.98; H, 4.14; N, 10.43; S, 15.94.

***N*-(5-Isopropyl-3-methyl-4-trifluoromethyl-1,3-thiazol-2(3*H*)-2-ylidene)-3-nitrobenzenesulfonamide (9a):** mp 127–128°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.31 (6H, d, $J = 7.0$ Hz), 3.53 (1H, m), 3.58 (3H, br s), 7.70 (1H, t, $J = 7.8$ Hz), 8.30 (1H, dt, $J = 2.0$, 7.8 Hz), 8.39 (1H, m), 8.79 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 410 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{14}F_3N_3O_4S_2$: C, 41.07; H, 3.45; N, 10.26; S, 15.66; F, 13.92. Found: C, 41.02; H, 3.37; N, 10.23; S, 15.64; F, 13.83.

***N*-[5-*tert*-Butyl-4-(trifluoromethyl)-1,3-thiazol-2-yl]-*N*-methyl-3-nitrobenzenesulfonamide (9b):** mp 119–120°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.36 (6H, d, $J = 6.9$ Hz), 3.44 (3H, s), 3.51 (1H, heptet, $J = 6.9$ Hz), 7.78 (1H, t, $J = 7.8$ Hz), 8.14 (1H, m), 8.50 (1H, ddd, $J = 1.0$, 2.4, 8.3 Hz), 8.67 (1H, t, $J = 2.4$ Hz). FAB-MS m/z: 410 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{14}F_3N_3O_4S_2$: C, 41.07; H, 3.45; N, 10.26; S, 15.66; F, 13.92. Found: C, 41.03; H, 3.39; N, 10.21; S, 15.72; F, 13.88.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)benzenesulfonamide (10a):** mp 188–189°C (ethyl acetate–hexane). ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s), 2.26 (3H, s), 3.40 (3H, s), 7.54 (3H, m), 7.82 (2H, m). FAB-MS m/z: 325 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{18}N_2O_2S_2$: C, 54.17; H, 5.84; N, 9.02; S, 20.66. Found: C, 54.00; H, 5.94; N, 8.95; S, 20.53.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-2-nitrobenzenesulfonamide (11a):** mp 138–139°C. ^{1}H NMR ($CDCl_3$) δ: 1.36 (9H, s), 2.28 (3H, s), 3.45 (3H, s), 7.61 (3H, m), 8.25 (1H, m). FAB-MS m/z: 370 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{19}N_3O_4S_2$: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.76; H, 4.99; N, 11.38; S, 17.69.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-4-nitrobenzenesulfonamide (12a):** mp 184–185°C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 2.27 (3H, s), 3.46 (3H, s), 8.15 (2H, dt, $J = 2.4$, 8.8 Hz), 8.29 (2H, dt, $J = 2.4$, 8.8 Hz). FAB-MS m/z: 370 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{19}N_3O_4S_2$: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.70; H, 4.98; N, 11.51; S, 17.43.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-methoxybenzenesulfonamide (13a):** mp 192–193°C (diethyl ether). ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s), 2.27 (3H, s), 3.40 (3H, s), 3.81 (3H, s), 7.14 (1H, ddd, $J = 1.0$, 2.5, 7.8 Hz), 7.29 (1H, t, $J = 2.5$ Hz), 7.39 (1H, br d, $J = 7.8$ Hz), 7.44 (1H, t, $J = 7.8$ Hz). FAB-MS m/z: 355 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{22}N_2O_3S_2$: C, 54.21; H, 6.26; N, 7.90; S, 18.09. Found: C, 54.31; H, 6.25; N, 7.86; S, 18.17.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-chlorobenzenesulfonamide (14a):** mp 138–139°C (chloroform). ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s), 2.28 (3H, s), 3.42 (3H, s), 7.57 (1H, dd, $J = 7.8$, 8.3 Hz), 7.66 (1H, ddd, $J = 1.0$, 2.0, 8.3 Hz), 7.79 (1H, br s), 7.80 (1H, br d, $J = 7.8$ Hz).

FAB-MS m/z: 359 ($M^+ + 1$). Anal. calcd. for $C_{15}H_{19}ClN_2O_2S_2Cl$: C, 50.20; H, 5.34; N, 7.81; S, 17.87; Cl, 9.88. Found: C, 50.01; H, 5.26; N, 7.76; S, 18.00; Cl, 10.04.

***N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-nitrobenzamide (15a):** mp 212–213°C (chloroform). ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.43 (3H, s), 3.84 (3H, s), 7.60 (1H, t, $J = 7.3$ Hz), 8.31 (1H, ddd, $J = 1.4$, 2.0, 7.3 Hz), 8.61 (1H, dt, $J = 1.4$, 7.3 Hz), 9.46 (1H, t, $J = 2.0$ Hz). FAB-MS m/z: 334 ($M^+ + 1$). Anal. calcd. for $C_{14}H_{24}N_2O_2S$: C, 57.64; H, 5.74; N, 12.60; S, 9.62. Found: C, 57.41; H, 5.64; N, 12.45; S, 9.61.

***N*′-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-*N*-methyl-*N*-(3-nitrophenyl)urea (16a):** mp 136–137°C (chloroform). ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 2.29 (3H, s), 3.45 (3H, s), 3.53 (3H, s), 7.45 (1H, t, $J = 8.3$ Hz), 7.74 (1H, br d, $J = 8.3$ Hz), 7.94 (1H, dd, $J = 1.9$, 8.3 Hz), 8.39 (1H, t, $J = 1.9$ Hz). FAB-MS m/z: 363 ($M^+ + 1$). Anal. calcd. for $C_{17}H_{22}N_4O_3S$: C, 56.33; H, 6.12; N, 15.46; S, 8.85. Found: C, 56.17; H, 6.02; N, 15.36; S, 8.86.

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