

## REGIOSPECIFIC ALKYLATION OF 5-SUBSTITUTED 2-ACYLAMINO-1,3,4-THIADIAZOLES

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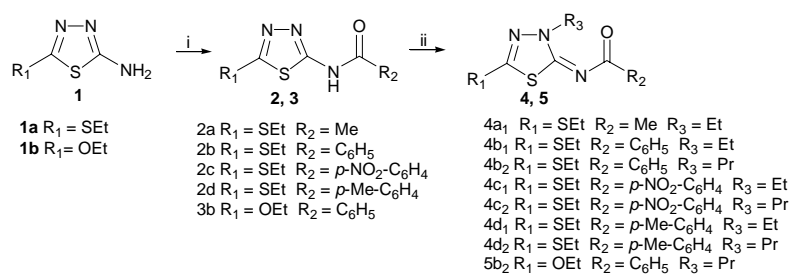
**Abstract-** 5-Substituted 2-acylamino-1,3,4-thiadiazoles (**2** and **3b**) are quantitatively and regiospecifically alkylated with alkyl bromide at the 3-position nitrogen (*endo*-products) rather than at the 2-position amide-nitrogen (*exo*-products) under basic conditions. This alkylation required more than 1.5 equivalents of base and more than four equivalents of alkyl bromide. The structures of the products, 5-substituted 2-acylimino-3-alkyl-1,3,4-thiadiazolines (**4** and **5b<sub>2</sub>**), were clearly established by spectroscopic data. Especially, the structure of 3-ethyl-5-ethylthio-2-*p*-toluoylimino-1,3,4-thiadiazoline (**4d<sub>1</sub>**) was proven by X-Ray crystallography.

### INTRODUCTION

2-Amino-1,3,4-thiadiazoles have received much attention in view of their biological<sup>1</sup> and analytical<sup>2</sup> interest. 2-Amino-1,3,4-thiadiazoles are ambident compounds; thus, their acylation and alkylation might take place at either the exocyclic NH<sub>2</sub> or the endocyclic NH, depending on reaction conditions.<sup>3</sup> Acetylation and tosylation of 2-monosubstituted amino-1,3,4-thiadiazoles have been reported.<sup>4</sup> Both reactions eventually resulted in the same exocyclic products, although the two pathways are quite different. Acetylation gave 2-acylamino-1,3,4-thiadiazoles directly; while, tosylation yielded 3-tosyl-2-imino-1,3,4-thiadiazoles and these *endo*-products were isomerized to the final *exo*-products. In contrast, methylation of 2-acylamino-1,3,4-thiadiazoles yielded isomeric mixtures of *exo*- and *endo-N*-methylated products, as expected.<sup>5</sup> To prepare 2-acylimino-3-methyl-1,3,4-thiadiazoline-5-sulfonamides to test their biological activities,<sup>1f,5</sup> 2-acylamino-5-benzylthio-1,3,4-thiadiazoles were methylated, although the yields were rather low. Most studies of 2-amino-1,3,4-thiadiazoles deal with their synthesis, while very little is known about their reactivity. To gain more insight into the selectivity of the alkylation reaction of 2-acylamino-1,3,4-thiadiazoles, we decided to examine the alkylation of 2-acylamino-5-ethylthio-1,3,4-thiadiazoles (**2**) and 2-benzoylamino-5-ethoxy-1,3,4-thiadiazole (**3b**) under basic conditions.

## RESULT AND DISCUSSION

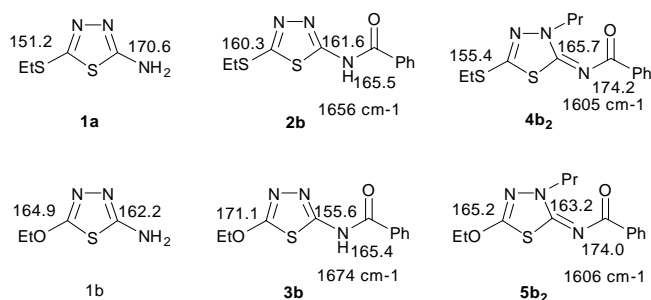
The substrates chosen for the alkylation study were 2-acylamino-5-ethylthio-1,3,4-thiadiazole (**2**)<sup>1f, 6</sup> and 2-benzoylamino-5-ethoxy-1,3,4-thiadiazole (**3b**).<sup>7-9</sup> To prepare the starting materials, the acylations of 2-amino-5-ethylthio-1,3,4-thiadiazole (**1a**) and 2-amino-5-ethoxy-1,3,4-thiadiazole (**1b**) were examined. Identical reactions took place at the 2-position NH<sub>2</sub> (*exo*-products), with quantitative yields like reactions of 2-monosubstituted amino-5-phenyl-1,3,4-thiadiazoles,<sup>4</sup> as shown in Scheme 1. The structure of the acylated product of **1b** was proven by comparison of spectroscopic data.<sup>9</sup> The spectrogram of an acylated product, 2-benzoylamino-5-ethoxy-1,3,4-thiadiazole (**3b**), was identical with the reported one. The structure of the acylated product of **1a** was confirmed *via* X-Ray crystallography. The structure of 5-ethylthio-2-*p*-toluoylamino-1,3,4-thiadiazoline (**2d**) shown in Figure 1 was clearly proven. The chemical shifts of the <sup>13</sup>C NMR peaks of **1a** and **2d** were assigned *via* HMBC (heteronuclear multiple bond coupling), as shown in Scheme 2.



Scheme 1. Reagents: i. R<sub>2</sub>COCl, TEA; THF; ii. R<sub>3</sub>Br, base.

The selective alkylation of **2**<sup>1f, 6</sup> and **3b**<sup>7-9</sup> was investigated under various basic conditions as shown in Table 1. The purity of the products was checked by HPLC. Surprisingly, under all basic conditions studied, alkylation yielded a single 3-alkylated *endo*-product. The alkylation product of 5-ethylthio-2-*p*-toluoylamino-1,3,4-thiadiazole (**2d**) was identified as 3-ethyl-5-ethylthio-2-*p*-toluoylimino-1,3,4-thiadiazoline (**4d<sub>1</sub>**) by X-Ray crystallography (Figure 2). To alkylate **2** and **3b** quantitatively, the base excess required is more than 1.5 equivalents and the alkyl halide required an excess of more than 4 equivalents as shown in Table 1. Under these conditions, the alkylated products are afforded quantitatively.

The structures of the products (2-acylimino-3-alkyl-5-ethylthio-1,3,4-thiadiazolines (**4**) and 2-benzoylimino-5-ethoxy-3-propyl-1,3,4-thiadiazoline (**5b<sub>2</sub>**)) were verified by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra. In the case of 2-benzoylimino-5-ethylthio-3-propyl-1,3,4-thiadiazoline (**4b<sub>2</sub>**), the IR spectrum is typically characterized by an imido group with strong bands at 1605 cm<sup>-1</sup> that are shifted to a shorter wave number than those of the amide (1656 cm<sup>-1</sup>) of the starting material (**2b**).<sup>5</sup> The same trend is apparent in 2-benzoylimino-3-propyl-5-ethoxy-1,3,4-thiadiazoline (**5b<sub>2</sub>**); in the IR spectrum, the imido group is seen at



Scheme 2.  $\delta_{\text{H}}$  (300 MHz; DMSO- $d_6$ ; Me $_4$ Si),  $\nu$  (KBr pellet).

Table 1. Propylation depending on reaction conditions.

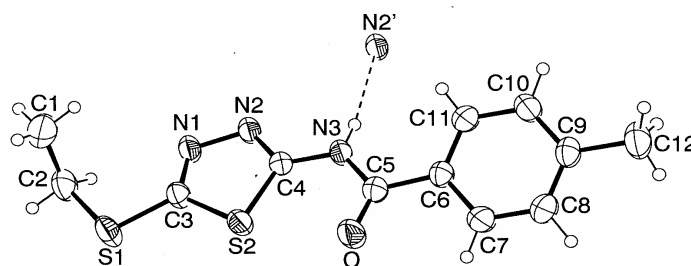
Starting Material	Solvent	Base (eq.)	Eq. Of PrBr	Yield (%)
<b>2b</b>	EtOH	KOH (1.5)	2.0	85
	EtOH	KOH (1.5)	4.0	90
	EtOH	KOH (2.0)	4.0	91
	EtOH	KOH (1.5)	Excess	97
	EtOH	Cs $_2$ CO $_3$ (1.5)	Excess	99 (93) <sup>a</sup>
	EtOH	Li $_2$ CO $_3$ (1.5)	Excess	98
	THF	Et $_3$ N (1.5)	4.0	72
	THF	Et $_3$ N (1.5)	Excess	96
<b>3b</b>	EtOH	KOH (1.5)	4.0	85 (78) <sup>a</sup>
	EtOH	KOH (1.5)	Excess	92
	EtOH	Li $_2$ CO $_3$ (1.5)	Excess	99

<sup>a</sup> Yields in parentheses are isolated ones .

1606  $\text{cm}^{-1}$ , which is shifted to a shorter wave number than the amide (1674  $\text{cm}^{-1}$ ) of 2-benzoyl-amino-5-ethoxy-1,3,4-thiadiazole (**3b**). The  $^{13}\text{C}$  NMR spectra of **4b $_2$**  and **5b $_2$**  were assigned by HMBC as shown in Scheme 2. The chemical shifts of C(2), C(5), and the carbonyl carbon of 2-benzoylimino-5-ethylthio-3-propyl-1,3,4-thiadiazoline (**4b $_2$** ) appear at 165.7, 155.4, and 174.2 ppm, respectively. If the alkylation takes place at the 2-position (*exo*-product), the chemical shifts of C(2) and C(5) of the product are more or less similar to the chemical shifts of 2-benzoylamino-5-ethylthio-1,3,4-thiadiazole (**2b**).

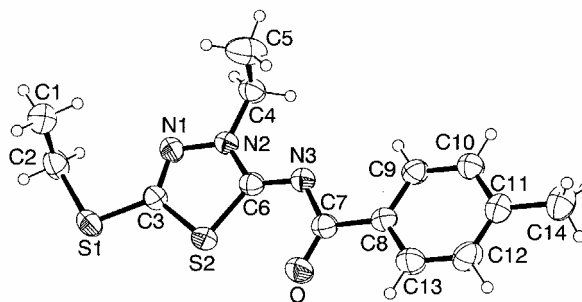
However, the chemical shifts of C(2) of the alkylated products are shifted at a lower field than the amide starting material by 5 ppm.<sup>5</sup> The same trend is also demonstrated between 2-benzoylimino-5-ethoxy-3-propyl-1,3,4-thiadiazoline (**5b $_2$** ) and 2-benzoylimino-5-ethoxy-1,3,4-thiadiazole (**3b**). The chemical shifts of C(2), C(5), and the carbonyl carbon of **5b $_2$**  appear at 163.2, 165.2, and 174.0 ppm, respectively.

Figure 1. The molecular structure of 5-ethylthio-2-*p*-toluoylamino-1,3,4-thiadiazole (**2d**), showing the atomic numbering used for the crystallographic analysis.



The chemical shift of C(2) of the alkylated product is 6 ppm lower than that of the starting material. These identical spectroscopic trends, including the IR spectral data, the hypothesis that the alkylation of 2-benzoylamino-5-ethoxy-1,3,4-thiadiazole (**3b**) takes place exclusively at the 3-position of nitrogen, like that of 2-acylamino-5-ethylthio-1,3,4-thiadiazole (**2**).

Figure 2. The molecular structure of 3-ethyl-2-ethylthio-5-*p*-toluoylimino-1,3,4-thiadiazoline (**4d<sub>1</sub>**), showing the atomic numbering used for the crystallographic analysis



## EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a Jasco Report-100 spectrophotometer. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained using a IBM-Bruker DRX 300 spectrometer (Korea Basic Science Institute, Taeduk, Taejon) at 300 MHz and 75 MHz respectively with tetramethylsilane as internal reference. The progresses of reaction and purity of products were traced with TLC and HPLC. Analytical RP-HPLC was performed to check the purity of products on  $\mu$  Bondapak  $\text{C}_{18}$  column (3.9 x 300 mm, 10  $\mu\text{m}$ ) using Waters 510 pump and UV detector ( $\lambda = 254$  nm). Elution condition; MeOH :  $\text{CH}_3\text{CN} = 5 : 95$  (v/v), flow rate 0.5 mL/min. 2-Amino-5-ethylthio-1,3,4-thiadiazole (**1a**)<sup>6,10</sup> and 2-amino-5-ethoxy-1,3,4-thiadiazole (**1b**)<sup>8,9</sup> was prepared as previously reported.

**2-Amino-5-ethylthio-1,3,4-thiadiazole (1a).**<sup>10</sup> mp 136-138 °C (lit.,<sup>6</sup> 133 °C, lit.,<sup>10</sup> 134-136 °C ),  $R_f$  0.59 (*n*-hexane : ethyl acetate : EtOH = 5 : 3 : 1).  $\nu_{\text{max}}$  (KBr)/  $\text{cm}^{-1}$ : 3250, 3100, 1620, 1520, 1420, 1080, 1050;  $\delta_{\text{H}}$  (300 MHz, DMSO- $d_6$ ): 7.27 (2H, br,  $\text{NH}_2$ ), 3.03 (2H, q,  $J = 7.2$  Hz,  $\text{SCH}_2$ ), 1.27 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz, DMSO- $d_6$ ): 170.6 (N-C=N), 151.2 (S-C-S), 29.9( $\text{CH}_2$ ), 16.0 ( $\text{CH}_3$ ).

## Acylation of 2-Amino-5-ethylthio-1,3,4-thiadiazole (1a) and 2-Amino-5-ethoxy-1,3,4-thiadiazole (1b).

### General Method

To a solution of compound **1** (1.55 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in dry THF (80 mL) was added a solution of acid chloride (20 mmol) in dry THF (20 mL). The reaction mixture was stirred at rt for 3 h. The solvent was evaporated under the reduced pressure to leave a solid residue, which was washed with water and *n*-hexane. The crude product was recrystallized from appropriate solvent.

### 2-Acetylamimo-5-ethylthio-1,3,4-thiadiazole (2a).

Yield (84%, after recrystallization from methanol), mp 194-196 °C (lit.,<sup>6</sup> 185 °C),  $R_f$  0.68 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1).  $\nu_{\max}$  (KBr)/  $\text{cm}^{-1}$ : 3150, 3050, 2950, 2800, 1700 (C=O), 1580, 1400;  $\delta_H$  (300 MHz, DMSO- $d_6$ ): 13.34 (1H, br, NH), 3.23 (2H, q,  $J = 7.2$  Hz, SCH<sub>2</sub>), 2.47 (3H, s, CH<sub>3</sub>CO), 1.45 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, DMSO- $d_6$ ): 169.5 (C=O), 161.5 (N-C=N), 161.0 (S-C-S), 29.5 (SCH<sub>2</sub>), 23.7 (CH<sub>3</sub>CO), 15.4 (CH<sub>3</sub>). Anal. Calcd. for C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>OS<sub>2</sub>: C, 35.75; H, 4.49; N, 21.21; S, 32.66. Found: C, 35.45; H, 4.46; N, 20.67; S, 31.55.

### 2-Benzoylamimo-5-ethylthio-1,3,4-thiadiazole (2b).

Yield (82%, after recrystallization from methanol), mp 144-146 °C,  $R_f$  0.73 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1).  $\nu_{\max}$  (KBr)/  $\text{cm}^{-1}$ : 3159, 1656 (C=O), 1531;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 13.02 (1H, br, NH), 8.28-8.26 (2H, m, Ph), 7.70-7.48 (3H, m, Ph), 3.24 (2H, q,  $J = 8$  Hz, SCH<sub>2</sub>), 1.42 (3H, t,  $J = 8$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 165.5 (C=O), 161.6 (N-C=N), 160.3 (S-C-S), 133.1, 131.0, 128.8, 128.7 (Ph), 28.2 (SCH<sub>2</sub>), 14.8 (CH<sub>3</sub>). Anal. Calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>OS<sub>2</sub>: C, 49.79; H, 4.18; N, 15.84; S, 24.17. Found: C, 50.27; H, 4.22; N, 16.70; S, 24.67.

### 5-Ethylthio-2-*p*-nitrobenzoylamimo-1,3,4-thiadiazole (2c).

Yield (84%, after recrystallization from THF), mp 255-256°C,  $R_f$  0.22 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/  $\text{cm}^{-1}$ : 3130, 1686 (C=O), 1527;  $\delta_H$  (300 MHz, DMSO- $d_6$ ): 13.53 (1H, br, NH), 8.39-8.37 (2H, m, Ph), 8.32-8.30 (2H, m, Ph), 3.27 (2H, q,  $J = 7.2$  Hz, SCH<sub>2</sub>), 1.38 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, DMSO- $d_6$ ): 165.2 (C=O), 160.5 (N-C=N), 160.3 (S-C-S), 151.0, 138.3, 131.1, 124.8 (Ph), 29.1 (SCH<sub>2</sub>), 15.6 (CH<sub>3</sub>). Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>: C, 42.57; H, 3.25; N, 18.08; S, 20.66. Found: C, 43.07; H, 3.31; N, 18.88; S, 21.01.

### 5-Ethylthio-2-*p*-toluoylamimo-1,3,4-thiadiazole (2d).

Yield (88%, after recrystallization from methanol), mp 175-177°C,  $R_f$  0.33 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/  $\text{cm}^{-1}$ : 3172, 1667 (C=O), 1526;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 12.74 (1H, br, NH), 8.15 (2H, d,  $J = 8.4$  Hz, Ph), 7.31 (2H, d,  $J = 8.4$  Hz, Ph), 3.26 (2H, q,  $J = 7.2$  Hz, SCH<sub>2</sub>), 2.44 (3H, s, CH<sub>3</sub>Ph), 1.44 (3H,

t,  $J = 7.2$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 165.4 (C=O), 161.3 (N-C=N), 160.1 (S-C-S), 143.8, 129.4, 128.7, 128.2 (Ph), 28.2 (SCH<sub>2</sub>), 21.7 (CH<sub>3</sub>Ph), 14.8 (CH<sub>3</sub>).

### **2-Benzoylamino-5-ethoxy-1,3,4-thiadiazole (3b).**

Yield (84% after recrystallization from ethanol), mp 184-185 °C,  $R_f$  0.7 (*n*-hexane : ethyl acetate : ethanol = 5 : 3 : 1).  $\nu_{max}$  (KBr)/ cm<sup>-1</sup>: 2992, 1674 (C=O), 1604, 1559, 1507;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>): 12.74 (1H, br, NH), 8.28-8.25 (2H, m, Ph), 7.62-7.41 (3H, m, Ph), 4.51 (2H, q,  $J = 7.1$  Hz, OCH<sub>2</sub>), 1.48 (3H, t,  $J = 7.1$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>): 171.1 (O-C-S), 165.4 (C=O), 155.6 (N-C=N), 132.9, 131.2, 128.8, 128.6 (Ph), 68.1 (OCH<sub>2</sub>), 14.5 (CH<sub>3</sub>). Anal. Calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 53.56; H, 4.51; N, 17.65; S, 12.96.

## **Regiospecific Alkylation of 2-Acylamino-5-ethylthio-1,3,4-thiadiazole (2) and 2-Benzoylamino-5-ethoxy-1,3,4-thiadiazole (3b).**

### **General Method**

Compound **2** (2 mmol) was dissolved in 50 mL of an appropriate solvent with base. An alkyl bromide was added to the solution. The resulting mixture was refluxed with stirring for 24 h. The solvent was evaporated under the reduced pressure. The residue was dissolved in *n*-hexane to filter off the insoluble materials. *n*-Hexane was evaporated in rotary evaporator and the crude product was crystallized from an appropriate solvent.

### **2-Acetylimino-3-ethyl-5-ethylthio-1,3,4-thiadiazoline (4a<sub>1</sub>).**

mp 41-43°C (recrystallization from diethyl ether),  $R_f$  0.83 (*n*-hexane : ethyl acetate = 5 : 5).  $\nu_{max}$  (KBr)/ cm<sup>-1</sup>: 2950, 1620 (C=O), 1500;  $\delta_H$  (300 MHz, DMSO-d<sub>6</sub>): 4.25 (2H, q,  $J = 7.2$  Hz, NCH<sub>2</sub>), 3.24 (2H, q,  $J = 7.2$  Hz, SCH<sub>2</sub>), 2.20 (3H, s, CH<sub>3</sub>CO), 1.32 (3H, t,  $J = 7.2$ , CH<sub>3</sub>), 1.28 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, DMSO-d<sub>6</sub>): 180.2 (C=O), 165.5 (N-C=N), 155.6 (S-C-S), 46.8 (NCH<sub>2</sub>), 28.3 (SCH<sub>2</sub>), 27.5 (CH<sub>3</sub>CO), 15.7 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>).

### **2-Benzoylimino-3-ethyl-5-ethylthio-1,3,4-thiadiazoline (4b<sub>1</sub>).**

mp 108-110°C (recrystallization from methanol),  $R_f$  0.75 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{max}$  (KBr)/ cm<sup>-1</sup>: 2970, 1603 (C=O), 1565;  $\delta_H$  (300 MHz, acetone-d<sub>6</sub>): 8.33-8.30 (2H, m, Ph), 7.58-7.47 (3H, m, Ph), 4.53 (2H, q,  $J = 7.2$  Hz, NCH<sub>2</sub>), 3.28 (2H, q,  $J = 7.2$  Hz, SCH<sub>2</sub>), 1.49 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>), 1.44 (3H, t,  $J = 7.2$  Hz, CH<sub>3</sub>);  $\delta_C$  (75 MHz, acetone-d<sub>6</sub>): 174.3 (C=O), 165.9 (N-C=N), 156.0 (S-C-S), 137.1, 132.9, 130.1, 129.0 (Ph), 47.0 (NCH<sub>2</sub>), 28.2 (SCH<sub>2</sub>), 15.0, (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>). Anal. Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>OS<sub>2</sub>: C, 53.22; H, 5.15; N, 14.32; S, 21.86. Found: C, 53.38; H, 5.21; N, 14.82; S, 21.93.

**2-Benzoylimimo-5-ethylthio-3-propyl-1,3,4-thiadiazoline (4b<sub>2</sub>).**

mp 58-59°C (recrystallization from diethyl ether),  $R_f$  0.83 (*n*-hexane: ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/ $\text{cm}^{-1}$ : 2965, 1605 (C=O), 1571;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ): 8.34-8.32 (2H, m, Ph), 7.57-7.44 (3H, m, Ph), 4.42 (2H, t,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 3.18 (2H, q,  $J = 7.3$  Hz,  $\text{SCH}_2$ ), 1.97 (2H, sextet,  $J = 7.2$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 1.45 (3H, t,  $J = 7.3$  Hz,  $\text{SCH}_2\text{CH}_3$ ), 1.02 (3H, t,  $J = 7.2$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ): 174.2 (C=O), 165.7 (N-C=N), 155.4 (S-C-S), 136.0, 132.0, 129.4, 128.1 (Ph), 52.7 ( $\text{NCH}_2$ ), 27.7 ( $\text{SCH}_2$ ), 21.9 ( $\text{NCH}_2\text{CH}_2$ ), 14.7, ( $\text{SCH}_2\text{CH}_3$ ), 11.2 ( $\text{NCH}_2\text{CH}_2\text{CH}_3$ ). Anal. Calcd. for  $\text{C}_{14}\text{H}_{17}\text{N}_3\text{OS}_2$ : C, 54.69; H, 5.57; N, 13.67; S, 20.86. Found: C, 54.71; H, 5.69; N, 13.45; S, 20.35.

**3-Ethyl-5-ethylthio-2-*p*-nitrobenzoylimimo-1,3,4-thiadiazoline (4c<sub>1</sub>).**

mp 125-127°C (recrystallization from diethyl ether),  $R_f$  0.75 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/ $\text{cm}^{-1}$ : 2975, 1617 (C=O), 1582;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ): 8.48-8.44 (2H, m, Ph), 8.31-8.28 (2H, m, Ph), 4.53 (2H, q,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 3.22 (2H, q,  $J = 7.2$  Hz,  $\text{CH}_2$ ), 1.54 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.47 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ): 172.1 (C=O), 165.8 (N-C=N), 156.6 (S-C-S), 149.9, 141.5, 130.3, 123.3 (Ph), 46.6 ( $\text{NCH}_2$ ), 27.6, ( $\text{SCH}_2$ ), 14.6 ( $\text{CH}_3$ ), 13.7 ( $\text{CH}_3$ ). Anal. Calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_3\text{S}_2$ : C, 46.14; H, 4.17; N, 16.56; S, 18.95. Found: C, 46.18; H, 4.17; N, 16.84; S, 19.11.

**2-Ethylthio-5-*p*-nitrobenzoylimimo-3-propyl-1,3,4-thiadiazoline (4c<sub>2</sub>).**

mp 111-112°C (recrystallization from *n*-hexane),  $R_f$  0.75 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/ $\text{cm}^{-1}$ : 2933, 1617 (C=O), 1584;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ): 8.45-8.42 (2H, m, Ph), 8.29-8.26 (2H, m, Ph), 4.44 (2H, t,  $J = 7.4$  Hz,  $\text{NCH}_2$ ), 3.21 (2H, q,  $J = 7.4$  Hz,  $\text{SCH}_2$ ), 1.99 (2H, sextet,  $J = 7.4$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 1.46 (3H, t,  $J = 7.4$  Hz,  $\text{SCH}_2\text{CH}_3$ ), 1.03 (3H, t,  $J = 7.4$  Hz,  $\text{NCH}_2\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ): 172.0 (C=O), 166.2 (N-C=N), 156.4 (S-C-S), 149.8, 141.5, 130.2, 123.2 (Ph), 52.9 ( $\text{NCH}_2$ ), 27.7 ( $\text{SCH}_2$ ), 21.8 ( $\text{NCH}_2\text{CH}_2$ ), 14.5, ( $\text{SCH}_2\text{CH}_3$ ), 11.1 ( $\text{NCH}_2\text{CH}_2\text{CH}_3$ ). Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3\text{S}_2$ : C, 47.71; H, 4.58; N, 15.90; S, 18.20. Found: C, 48.33; H, 4.64; N, 16.04; S, 18.33.

**3-Ethyl-5-ethylthio-2-*p*-toluoylimimo-1,3,4-thiadiazoline (4d<sub>1</sub>).**

mp 95-97°C (recrystallization from diethyl ether),  $R_f$  0.75 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/ $\text{cm}^{-1}$ : 2968, 1603 (C=O), 1563;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ): 8.21 (2H, d,  $J = 8$  Hz, Ph), 7.25 (2H, d,  $J = 8$  Hz, Ph), 4.49 (2H, q,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 3.18 (2H, q,  $J = 7.2$  Hz,  $\text{SCH}_2$ ), 2.41 (3H, s,  $\text{CH}_3\text{Ph}$ ), 1.50 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.44 (3H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ): 174.1 (C=O), 165.0 (N-C=N), 155.4 (S-C-S), 142.5, 133.3, 129.5, 128.8 (Ph), 46.2 ( $\text{NCH}_2$ ), 27.7 ( $\text{SCH}_2$ ), 21.6 ( $\text{CH}_3\text{Ph}$ ), 14.6 ( $\text{CH}_3$ ), 13.6 ( $\text{CH}_3$ ).

**5-Ethylthio-3-propyl-2-*p*-toluoylimimo-1,3,4-thiadiazoline (4d<sub>2</sub>).**

mp 83-85°C (recrystallization from diethyl ether),  $R_f$  0.83 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\max}$  (KBr)/

cm<sup>-1</sup>: 2963, 1604, 1562;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>): 8.20 (2H, d,  $J = 8$  Hz, Ph), 7.24 (2H, d,  $J = 8$  Hz, Ph), 4.40 (2H, t,  $J = 7.4$  Hz, NCH<sub>2</sub>), 3.16 (2H, q,  $J = 7.4$  Hz, SCH<sub>2</sub>), 2.41 (3H, s, CH<sub>3</sub>Ph), 1.96 (2H, sextet,  $J = 7.4$  Hz, NCH<sub>2</sub>CH<sub>2</sub>), 1.43 (3H, t,  $J = 7.4$  Hz, SCH<sub>2</sub>CH<sub>3</sub>), 1.00 (3H, t,  $J = 7.4$  Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>): 174.1 (C=O), 165.5 (N-C=N), 155.2 (S-C-S), 142.4, 133.3, 129.4, 128.8 (Ph), 52.6 (NCH<sub>2</sub>), 27.7 (SCH<sub>2</sub>), 21.8 (CH<sub>3</sub>Ph), 21.6 (NCH<sub>2</sub>CH<sub>2</sub>), 14.6, (SCH<sub>2</sub>CH<sub>3</sub>), 11.1 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>OS<sub>2</sub>: C, 56.04; H, 5.96; N, 13.07; S, 19.95. Found: C, 57.06; H, 6.08; N, 13.30; S, 19.97.

### **2-Benzylimino-5-ethoxy-3-propyl-1,3,4-thiadiazoline (5b<sub>2</sub>).**

mp 87-88°C (recrystallization from diethyl ether),  $R_f$  0.81 (*n*-hexane : ethyl acetate = 7 : 3).  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup>: 2962, 1606 (C=O), 1570, 1505;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>): 8.31-8.29 (2H, m, Ph), 7.60-7.42 (3H, m, Ph), 4.41 (2H, q,  $J = 7.1$  Hz, OCH<sub>2</sub>), 4.31 (2H,  $J = 7.4$  Hz, NCH<sub>2</sub>), 1.92 (2H, sextet,  $J = 7.4$  Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.45 (3H, t,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.00 (3H, t,  $J = 7.4$  Hz, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>): 174.0 (C=O), 165.2 (O-C-S), 163.2 (N-C=N), 136.2, 131.8, 129.3, 128.1 (Ph), 67.7 (OCH<sub>2</sub>), 52.1 (NCH<sub>2</sub>), 21.7 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 14.3 (OCH<sub>2</sub>CH<sub>3</sub>), 11.2 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 57.71; H, 5.88; N, 14.42; S, 11.01. Found: C, 58.16; H, 5.94; N, 14.83; S, 11.29.

### **X-Ray Crystallographic Analysis of 5-Ethylthio-2-*p*-toluoylamino-1,3,4-thiadiazole (2d).**

Direct methods (SHELX86)<sup>11</sup> (all non-H atoms) followed by full-matrix least-squares refinement (SHELX97)<sup>12</sup> on  $F^2$  with all non-H atoms anisotropic. Hydrogen atoms were located from  $\Delta F$  synthesis and positionally refined. Final  $R_1$  [ $F \geq 2\sigma(F)$ ] and  $wR_2$  [all data] were 0.0446 and 0.0978 for 202 refined parameters,  $S[F^2]$  1.029. And  $(\Delta/\delta)_{\text{max}}$  was 0.000. Maximum and minimum features in  $\Delta F$  synthesis are 0.180 and -0.199 e $\text{\AA}^{-3}$ , respectively.

### **X-Ray Crystallographic Analysis of 3-Ethyl-5-ethylthio-2-*p*-toluoylimino-1,3,4-thiadiazoline (4d<sub>1</sub>).**

The structure was determined by the same procedure previously applied for the structure determination of **2d**. Final  $R_1$  [ $F \geq 2\sigma(F)$ ] and  $wR_2$  [all data] were 0.0457 and 0.1011 for 233 refined parameters,  $S[F^2]$  1.030. And  $(\Delta/\delta)_{\text{max}}$  was 0.000. Maximum and minimum features in  $\Delta F$  synthesis are 0.210 and -0.187 e $\text{\AA}^{-3}$ , respectively.

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