

REGIOSELECTIVE CYCLOCONDENSATIONS OF  
CHLOROCARBONYLSULFENYL CHLORIDE WITH  
HYDRAZONES: EFFECTIVE SYNTHESIS OF A CLASS OF  
SULFUR AND NITROGEN CONTAINING HETEROCYCLES  
WITH -COS- LINKAGE

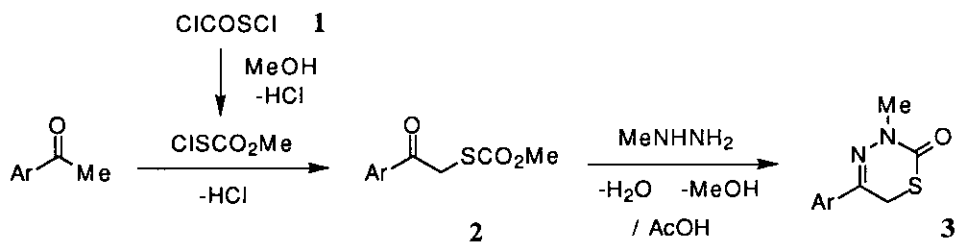
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**Abstract** - Regioselective cyclocondensations of several hydrazones with chlorocarbonylsulfenyl chloride afforded 1,3,4-(3*H*,6*H*)-thiadiazin-2-one derivatives and 3(2*H*)-(dimethylamino)thiazolones. The -COS- linkage was effectively incorporated into the *S*, *N*-containing heterocycles.

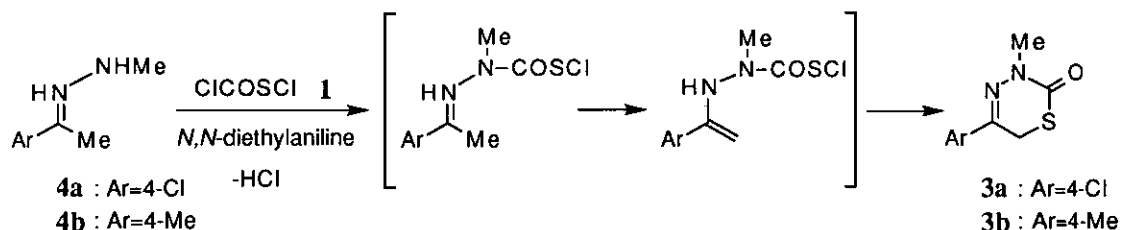
The electrophilic bifunctional reagents such as chlorosulfonyl isocyanate (ClSO<sub>2</sub>NCO)<sup>1</sup> and chlorocarbonylsulfenyl chloride (ClCOSCl; abbreviated CCSC; 1)<sup>2</sup> used for cyclocondensation reactions are recognized as important synthetic building blocks for preparing heterocyclic sulfur- and/or nitrogen-containing compounds. During our continuing synthetic studies in search of *S*, *N*-containing heterocycles,<sup>3</sup> we have reported the effective and practical syntheses of 2(3*H*)-benzothiazolone derivatives employing CCSC (1).<sup>4,5</sup> Since some of these 2(3*H*)-benzothiazolones and 2(3*H*)-thiazolones comprise useful pesticides, medicines, and dyestuffs,<sup>4,6</sup> their synthesis is considered of practical importance. Recently, we have reported the regioselective preparation of  $\alpha$ -methoxycarbonylsulfenyl ketones and aldehydes (2), which serve as a favorite synthon for 2(3*H*)-thiazolones, 5-aryl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazine-2-ones (3) as an isoster of 2(3*H*)-thiazolones, and 3-thiolindoles.<sup>7</sup>

Sulfenyl compounds (2) are obtained by the coupling reaction between the corresponding ketones or

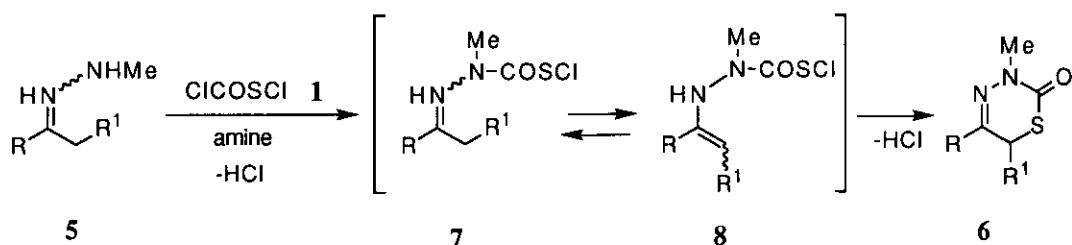


aldehydes and methoxycarbonylsulfonyl chloride which is prepared from CCSC (1) and methanol. However, this method for preparing **3** has the following drawbacks: (1) incorporation of key -COS- linkage requires stepwise condensation reactions; (2) substituent of 5-position and 6-position is only limited to aryl groups and hydrogen, respectively; and (3) somewhat harsh conditions (80 °C in AcOH solvent) are required to conduct this cyclocondensation.

To solve these problems, a more direct [2+4] cyclocondensation using CCSC (1) was examined. We now describe an alternative and more straightforward synthetic route for preparing 1,3,4-(3*H*,6*H*)-thiadiazin-2-ones; the one-pot cyclocondensation of methyl hydrazones (4) with CCSC (1) afforded 5-aryl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-ones (3) in better yields than the aforementioned method.



In addition, the present method is applicable to preparing 5,6-dialkyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-ones (6) from methyl hydrazones (5) possessing an aliphatic substituent (R and R<sup>1</sup>). Moreover, a new class of 3-aryl derivatives (10) could be obtained from aryl hydrazones (9) upon treatment with CCSC (1). These results are listed in Table 1.



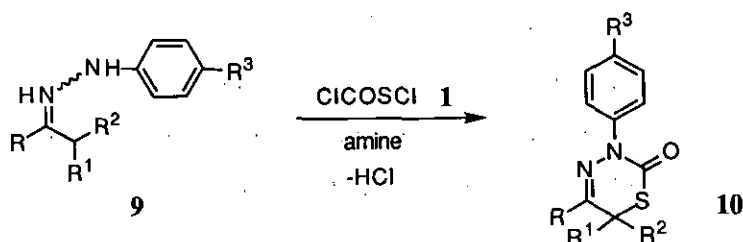


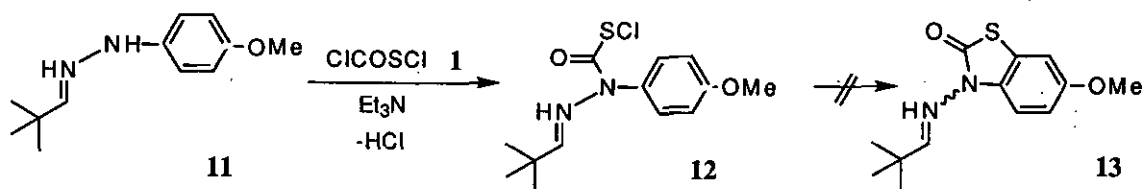
Table 1. Cyclocondensations of CCSC (1) with Methyl Hydrazones (5) and Aryl Hydrazones (9).<sup>a</sup>

Entry	Hydrazone	Hydrazone				Amine	Product	Yield / %
		R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>			
1	5a	H	PhCH <sub>2</sub>	--	--	Tributylamine	6a	42
2	5b	Me	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	--	--	<i>N,N</i> -Diethylaniline	6b <sup>b</sup>	31
3	5c	Pr	Et	--	--	<i>N,N</i> -Diethylaniline	6c	42
4	9a	<i>i</i> -Pr	Me	Me	MeO	<i>N,N</i> -Diethylaniline	10a	41
5	9b	<i>t</i> -Bu	H	H	MeO	<i>N,N</i> -Diethylaniline	10b	52

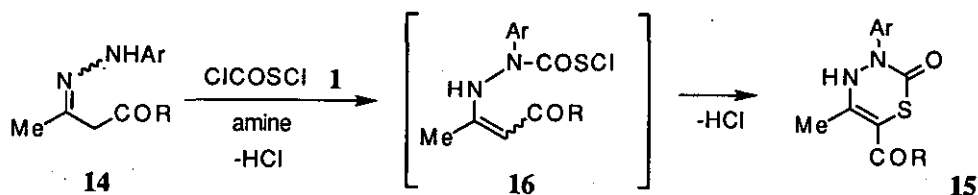
<sup>a</sup> The reactions were carried out at 0 °C-room temperature for 10 h. Molar ratio of 5 (or 9): 1 : amine = 1 : 1.1 : 1.1. <sup>b</sup> A regioisomer (R=*n*-C<sub>6</sub>H<sub>13</sub>; R<sup>1</sup>=R<sup>2</sup>=H) was contained in < 10%.

All three reactions using hydrazones (4, 5, and 9) proceeded smoothly under milder reaction conditions (using 1.1 equiv. of amine at 0 °C-room temperature in toluene or THF solvent) compared with those using 2. The amine as the HCl scavenger is considered to work in the acylation step, whose plausible mechanism is similar to the case of the previous synthesis of 2(3*H*)-benzothiazolones.<sup>4</sup> It is noted that this S-C bond formation proceeded with moderate regioselectivity (Table 1, Entry 2), i.e., in thermodynamically controlled manner, which is consistent with the tendency of  $\alpha$ -methoxycarbonylsulfonylation<sup>7</sup> and  $\alpha$ -thiocyanation of ketones.<sup>8</sup> Although hydrazones (5) are a mixture of the *E*- and *Z*-forms, it is postulated that the initial acylated hydrazone intermediate (7) can change by tautomerization to the reactive hydrazines intermediate (8), which in turn is able to undergo the desired cyclization.

Hydrazone (**11**) is apparently an unsuitable substrate for the present cyclocondensation. Nevertheless, we tested a similar reaction using **11** expecting the preparation of the corresponding 2(3*H*)-benzothiazolone (**13**).<sup>4</sup> This trial resulted only in the isolation of considerably stable sulfenyl chloride (**12**) in 80% yield, which did not cyclize to give **13** even with the aid of AlCl<sub>3</sub> or H<sub>2</sub>SO<sub>4</sub>.



We also found that aryl hydrazones (**14**), derived from active methylene compounds such as methyl acetoacetate and 2,4-pentanedione, more smoothly underwent this cyclocondensation to give 1,3,4-(3*H*,4*H*)-thiadiazin-2-ones (**15**) in better yields, the result of which could be accounted for easier formation of reactive intermediate (**16**). Being encouraged by these results, the use of the *N,N*-dimethylhydrazones of methyl acetoacetate (**17a**) and 2,4-pentanedione (**17b**) was next tried. Consequently, an alternative [2+3] cyclocondensation proceeded to afford 3(2*H*)-dimethylaminothiazol-2-ones (**18a** and **18b**) in good yields (~ 80%).

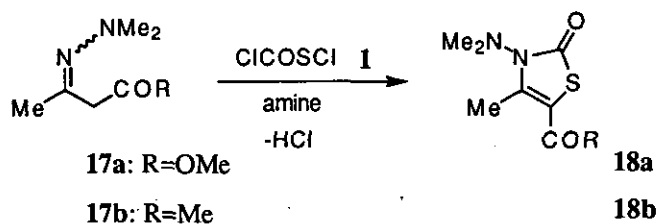


In conclusion, several types of cyclocondensation utilizing the characteristics of CCSC (**1**) are described. These cyclocondensation proceeded regioselectively and realized the preparation of a class of *S,N*-containing heterocycles with -COS- linkage.

**Table 2. Cyclocondensations of CCSC (1) with Hydrazones of Methyl Acetoacetate and 2,4-Pentanedione (14).<sup>a</sup>**

Entry	Hydrazones	Ar		Product	Yield / %
		Ar	R		
1	14a	Ph	OMe	15a	71
2	14b	Ph	Me	15b	66
3	14c	4-Cl-Ph	OMe	15c	58
4	14d	4-Me-Ph	OMe	15d	46

<sup>a</sup> The reactions were carried out using triethylamine as a base at 0 °C-room temperature for 10 h. Molar ratio of 14 : 1 : amine = 1 : 1.1 : 1.1.



## EXPERIMENTAL

All melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. <sup>1</sup>H Nmr spectra were recorded on a Hitachi R-24 B (60 MHz) or JEOL EX-90 (90 MHz) spectrometer using TMS as an internal standard in CDCl<sub>3</sub>. <sup>13</sup>C Nmr spectra were recorded on a JEOL α (400 MHz) spectrometer using TMS as an internal standard in CDCl<sub>3</sub>. Mass spectra were obtained on a Hitachi M-80 spectrometer. Ir spectra were recorded on a Hitachi 270-30 spectrophotometer. Silica gel column chromatography was performed on a Merck Art. 7734. Methyl- and arylhydrazones were prepared by the known procedure.<sup>9</sup>

### 5-(4-Chlorophenyl)-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (3a).

To a stirred solution of 4-chloroacetophenone methylhydrazone (183 mg, 1.0 mmol) and *N,N*-diethylaniline (164 mg, 1.1 mmol) in toluene (2.0 ml) was added CCSC (1, 144 mg, 1.1 mmol) at 0-5 °C.

The reaction mixture was allowed to warm to room temperature followed by being stirred for 10 h. 1M-HCl aqueous solution (20 ml) was added to the mixture, which was extracted with EtOAc (20 ml). The organic phase was washed with 1M-HCl aqueous solution, sat. aqueous NaHCO<sub>3</sub> solution, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated. The crude residue was purified by silica gel column chromatography (chloroform and/or hexane/ethyl acetate = 5:1) to give the desired compound (125 mg, 52 %). Colorless crystals; mp 156-157 °C (lit.,<sup>5</sup> 157-159 °C).

**5-(*p*-Tolyl)-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (3b).**

With a similar procedure as that for preparing 3a, the desired compound was obtained in 64 % yield. Colorless crystals; mp 94-96 °C (lit.,<sup>5</sup> 94-95 °C).

**6-Benzyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6a).**

With a similar procedure as that for preparing 3a, except using tributylamine as acid scavenger in place of *N,N*-diethylaniline, the desired compound was obtained. Yellow oil; Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>OS: C, 59.97; H, 5.49; N, 12.72. Found C, 59.69; H, 5.68; N, 12.44. <sup>1</sup>H Nmr δ=3.05 (1H, dd, *J*<sub>gem</sub> = 12 Hz, *J* = 2 Hz), 3.60 (1H, dd, *J*<sub>gem</sub> = 12 Hz, *J* = 2 Hz), 3.35 (3H, s), 3.80-4.05 (1H, m), 7.05 (1H, d, *J* = 3 Hz), 7.10-7.50 (5H, m); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>.

**6-Pentyl-3,5-dimethyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6b).**

With a similar procedure as that for preparing 3a, except using THF as solvent in place of toluene, the desired compound was obtained. Yellow oil; Anal. Calcd for C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>OS: C, 56.04; H, 8.46; N, 13.07. Found C, 55.88; H, 8.40; N, 12.91. <sup>1</sup>H Nmr δ=0.90 (3H, t, *J* = 7 Hz), 1.10-2.00 (6H, m), 2.15 (3H, s), 2.30-2.60 (2H, m), 3.25-3.40 (1H, m), 3.35 (3H, s); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>. A regioisomer of 6b i.e., 5-hexyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one: <sup>1</sup>H Nmr δ=0.90 (3H, t, *J* = 7 Hz), 1.10-2.00 (9H, m), 2.15 (3H, s), 2.30-2.60 (2H, m), 3.25-3.40 (1H, m), 3.35 (3H, s), 3.40 (2H, s); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>.

**6-Ethyl-3-methyl-5-propyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6c).**

With a similar procedure as that for preparing 6b, the desired compound was obtained. Yellow oil; Anal. Calcd for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>OS: C, 53.97; H, 8.05; N, 13.99. Found C, 53.78; H, 7.99; N, 13.74. <sup>1</sup>H Nmr δ=0.85-1.20 (6H, m), 1.40-1.95 (4H, m), 2.30-2.55 (2H, m), 3.20 (1H, dd, *J* = 10 Hz, 6 Hz), 3.40 (3H, s); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>.

**5-Isopropyl-3-(4-methoxyphenyl)-6,6-dimethyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one(10a).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Colorless crystals,

mp 98-99 °C ; Anal. Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S: C, 61.62; H, 6.89; N, 9.58. Found C, 61.62; H, 6.94; N, 9.64. <sup>1</sup>H Nmr δ=1.20 (6H, d, *J* = 7 Hz), 1.60 (6H, s), 2.65-3.00 (1H, m), 3.80 (3H, s), 6.90 (2H, d, *J* = 8 Hz), 7.40 (2H, d, *J* = 8 Hz); <sup>13</sup>C nmr δ=21.94, 25.94, 30.84, 45.15, 55.48, 113.86, 126.17, 134.62, 160.54; ms *m/z* 292 (M<sup>+</sup>); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>.

**5-(*tert*-Butyl)-3-(4-methoxyphenyl)-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (10b).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Colorless crystals, mp 115-117 °C ; Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S: C, 60.41; H, 6.52; N, 10.06. Found C, 60.41; H, 6.52; N, 9.91. <sup>1</sup>H Nmr δ=1.20 (9H, s), 3.50 (2H, s), 3.80 (3H, s), 6.90 (2H, d, *J* = 8 Hz), 7.40 (2H, d, *J* = 8 Hz); ir (film) ν<sub>max</sub>: 1720 cm<sup>-1</sup>.

**Trimethylacetaldehyde chlorosulfonylcarbonyl(4-methoxyphenyl)hydrazone (12).**

With a similar procedure as that for preparing 3a, 12 was obtained. Light brown crystals, mp 117-119 °C; Anal. Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>ClS: C, 51.91; H, 5.70; N, 9.31. Found C, 51.69; H, 5.71; N, 9.27. <sup>1</sup>H Nmr δ=1.10 (9H, s), 3.85 (3H, s), 6.75 (1H, s), 6.90-7.20 (4H, m); ms *m/z* 300 (M<sup>+</sup>).

**Methyl [3-phenyl-5-methyl-2-oxo-1,3,4-(3*H*,4*H*)thiadiazin-6-yl]carboxylate (15a).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Colorless crystals, mp 141-143 °C; Anal. Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: C, 54.53; H, 4.58; N, 10.60. Found C, 54.27; H, 4.51; N, 10.46. <sup>1</sup>H Nmr δ=2.55 (3H, s), 3.85 (3H, s), 6.55-7.35 (5H, m), 6.70-6.85 (1H, br s; -NH-); <sup>13</sup>C nmr δ=12.79, 52.19, 99.93, 113.23, 122.51, 129.52, 133.09, 145.29, 146.00, 170.05; ms *m/z* 264 (M<sup>+</sup>).

**6-Acetyl-3-phenyl-5-methyl-1,3,4-(3*H*,4*H*)thiadiazin-2-one (15b).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Yellow oil, Anal. Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S: C, 58.05; H, 4.87; N, 11.28. Found C, 57.88; H, 4.77; N, 11.05. <sup>1</sup>H Nmr δ=2.25 (3H, s), 2.30(3H, s), 7.25-7.50 (1H, br s; -NH-), 7.35-7.55 (5H, m); ms *m/z* 248 (M<sup>+</sup>); ir (film) ν<sub>max</sub>: 3250, 1725, 1650 cm<sup>-1</sup>.

**Methyl [3-(4-chlorophenyl)-5-methyl-2-oxo-1,3,4-(3*H*,4*H*)thiadiazin-6-yl]carboxylate (15c).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Colorless crystals, mp 142-144 °C; Anal. Calcd for C<sub>12</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>3</sub>S: C, 48.25; H, 3.71; N, 9.38. Found C, 48.01; H, 3.67; N, 9.56. <sup>1</sup>H Nmr δ=2.55 (3H, s), 3.85 (3H, s), 6.55 (2H, d, *J* = 12 Hz), 7.20 (2H, d, *J* = 12 Hz),

7.20-7.50 (1H, br s);  $^{13}\text{C}$  nmr  $\delta$ =13.50, 52.59, 100.64, 114.78, 127.74, 129.77, 144.26, 145.68, 162.04, 170.16; ir (KBr)  $\nu_{\text{max}}$ : 3250, 1726, 1658  $\text{cm}^{-1}$ .

**Methyl [5-methyl-2-oxo-3-(*p*-tolyl)-1,3,4-(3*H*,4*H*)-thiadiazin-6-yl]carboxylate (15d).**

With a similar procedure as that for preparing 3a, the desired compound was obtained. Colorless crystals, mp 185-186 °C; Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ : C, 56.10; H, 5.07; N, 10.06. Found C, 56.02; H, 4.98; N, 10.26.  $^1\text{H}$  Nmr  $\delta$ =2.25 (3H, s), 2.55 (3H, s), 3.85 (3H, s), 6.60 (2H, d,  $J = 10$  Hz), 7.10 (2H, d,  $J = 10$  Hz), 6.50-6.80 (1H, br s);  $^{13}\text{C}$  nmr  $\delta$ =12.74, 20.47, 52.10, 99.73, 113.25, 129.90, 131.74, 142.92, 145.86, 161.84, 169.79; ir (KBr)  $\nu_{\text{max}}$ : 3427, 1722, 1664  $\text{cm}^{-1}$ .

**Methyl [3-dimethylamino-4-methyl-2-oxo-2(3*H*)-thiazol-3-yl]carboxylate (18a).**

With a similar procedure as that for preparing 3a, the desired compound was obtained in 82% yield. Colorless crystals, mp 87.5-88.5 °C; Anal. Calcd for  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ : C, 44.43; H, 5.59; N, 12.95. Found C, 44.21; H, 5.42; N, 12.98.  $^1\text{H}$  Nmr  $\delta$ =2.50 (3H, s), 2.95 (6H, s), 3.80 (3H, s); ms  $m/z$  216 ( $\text{M}^+$ ), 173 ( $\text{M}^++1\text{-NMe}_2$ ).

**5-Acetyl-3-dimethylamino-4-methyl-2(3*H*)-thiazolone (18b).**

With a similar procedure as that for preparing 3a, the desired compound was obtained in 77% yield. Colorless crystals, mp 78-80 °C; Anal. Calcd for  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ : C, 47.98; H, 6.04; N, 13.99. Found C, 47.77; H, 5.97; N, 14.07.  $^1\text{H}$  Nmr  $\delta$ =2.25 (3H, s), 2.30(3H, s), 2.95 (6H, s); ms  $m/z$  200 ( $\text{M}^+$ ), 157 ( $\text{M}^++1\text{-NMe}_2$ ).

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