

Article

Syntheses of Diheterocyclic Compounds Based on 2-Thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]-pyrimidine

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Abstract: The syntheses of some diheterocyclic compounds from 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**) are described. Compound **1** can be converted into triazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles. The structures of the intermediates and the target compounds were confirmed by ¹H-NMR, MS and elemental analyses.

Keywords: 1,2,4-Triazolo[1,5-a]pyrimidine, triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazoles

Introduction

The study of nitrogen-containing heterocycles is currently a hot topic in pesticide chemistry [1-7]. In particular the chemistry of 1,2,4-triazolo[1,5-a]pyrimidine derivatives has been of considerable interest for many years [8]. In 1935, 5-methyl-7-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine was found to be an excellent stabilizer for photographic emulsions. Since then, various derivatives of 1,2,4-triazolo[1,5-a]pyrimidine have found applications in pharmaceutical and agricultural chemistry and other areas [9-10]. On the other hand, a wide range of biological activities have been attributed to compounds containing 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole and

1,2,4-triazole ring systems [11-14]. If these heterocycles are introduced into the 1,2,4-triazolo[1,5-a]-pyrimidine ring, the linked diheterocyclic compounds might display interesting biological activity, so as a part of our research work aimed at searching for novel agrochemicals, our interest in diheterocyclic compounds containing 1,2,4-triazolo[1,5-a]pyrimidine moieties lead us to study the syntheses of the some diheterocyclic compounds based on the use of 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**) as the starting material.

Results and Discussion

2-Thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**) was prepared according to our previous procedure [5]. At room temperature, compound **1** reacted with CS₂ in ethanol in the presence of potassium hydroxide, followed by treatment with hydrazine hydrate at reflux to afford compound **2**. The structure of **2** was confirmed by its ¹H-NMR spectrum and elemental analysis. The NMR spectrum showed the methylene, amino and mercapto group protons as three singlets, at δ 4.56 ppm (SCH₂), 5.66 ppm (NH₂) and 13.67 ppm (SH), respectively.

Alkylation of **2** with alkyl halides afforded compounds **3** in good yields, whose structures were confirmed by their ¹H-NMR spectra and elemental analysis. In ethanol solution and in the presence of HCl, **2** reacted with aromatic aldehydes to give a difused heterocyclic compound **4**. The pH value of the reaction solution influenced the yield of the product and experimental results showed that the best pH value was 4~6. In the ¹H-NMR spectrum of compound **4**, the signals of the NH and methenyl (SCH) groups were observed as two singlets at δ 13.7~14.0 ppm (NH) and 9.50~ 10.90 ppm (SCH), respectively. The presence of these NH and SCH signals demonstrated the formation of 5,6-dihydrogen-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole moiety.

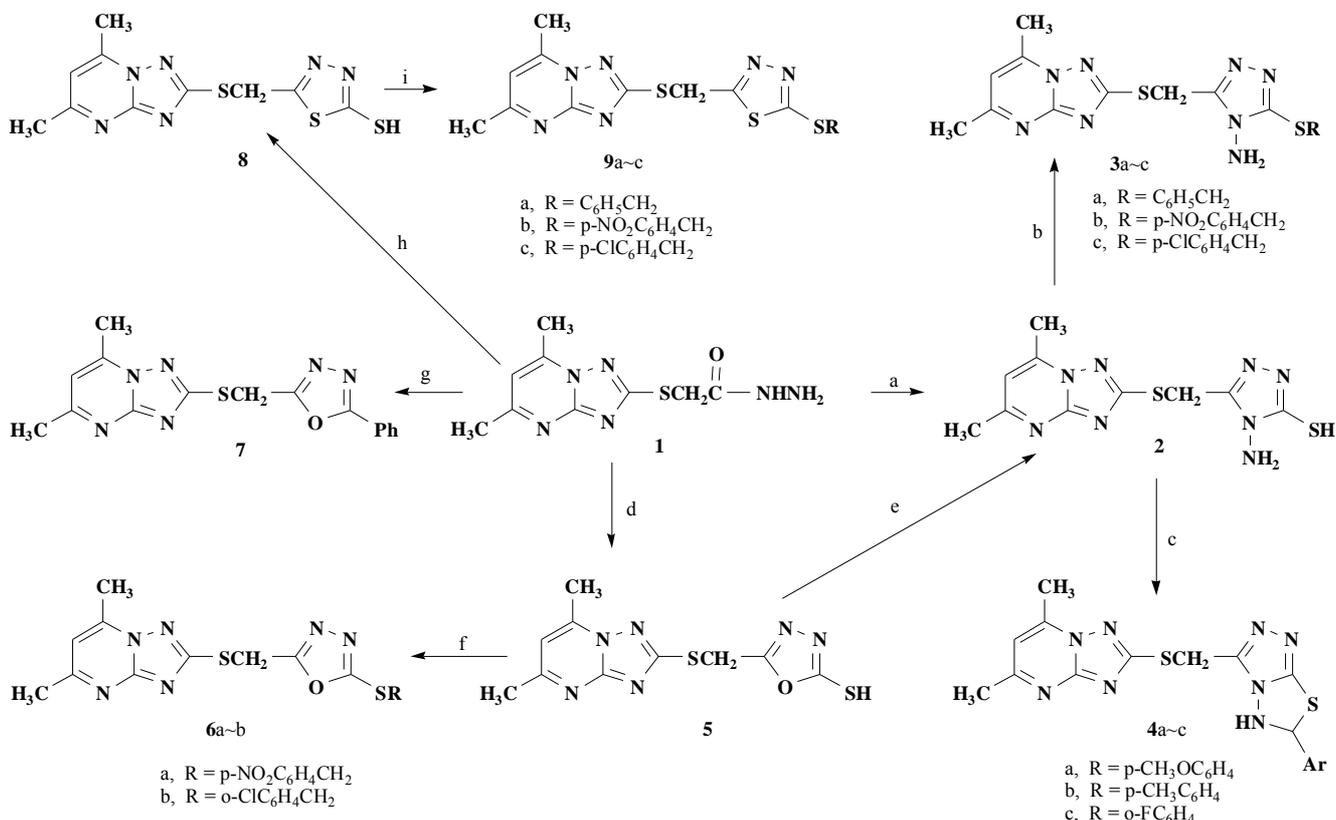
Compound **1** was also refluxed with carbon disulfide in ethanol in the presence of potassium hydroxide with subsequent treatment with hydrochloric acid. The ¹H-NMR spectrum and elemental analysis data of the isolated product were consistent with the 1,3,4-oxadiazole structure **5**. Compound **5** reacted with alkyl halides in the presence of sodium hydroxide to afford compounds **6**. The reaction of **5** with alkyl halides is a typical nucleophilic substitution process and the experimental results indicated that the reactivity of the alkyl halide determined the reaction time and the yields. For example, intermediate **5** reacted with *p*-nitrobenzyl chloride under basic conditions at room temperature to give compound **6a** in yield 56% after 2 hours, but no product was observed when intermediate **5** reacted with 1-bromocyclohexane under the same conditions. Interestingly, compound **2** can also be obtained in 42% yield by refluxing compound **5** with hydrazine hydrate in methanol.

Heating compound **1** with benzoic acid in the presence of phosphoryl chloride afforded diheterocyclic compound **7** in 66% yield. The structure of **7** was established by ¹H-NMR and elemental analysis. For example, the proton spectrum showed two methyl protons as two singlets at δ 2.64 ppm (5-CH₃) and 2.73 (7-CH₃), respectively. The SCH₂ group protons and 6-protons in the 1,2,4-triazolo-[1,5-a]pyrimidine moiety displayed two singlets at δ 4.82 ppm (SCH₂) and 6.76 ppm (6-H), respectively. The phenyl protons displayed a multiplet at δ 7.47-8.01 ppm (C₆H₅).

Furthermore, 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine **1** can react with carbon disulfide in ethanol in presence of potassium hydroxide at room temperature with subsequent treatment with concentrated H₂SO₄ to afford a cyclization product **8** containing a 1,3,4-thiadiazole

moiety, which was then alkylated with alkyl halides to give the corresponding compounds **9** in good yields. The factors affecting the yields and the reaction time for these alkylations of **8** were similar to those of the reaction of **5** with alkyl halides.

Scheme 1. Synthesis of diheterocyclic compounds based on compound **1**.



a: (i) CS₂, KOH, r.t.; (ii) NH₂NH₂.H₂O, reflux; b: RX, NaOH, r.t.; c: ArCHO, HCl, reflux; d: CS₂, KOH, reflux; e: NH₂NH₂.H₂O, reflux; f: RX, NaOH, r.t.; g: PhCOOH, POCl₃, reflux; h: (i) CS₂, KOH, r.t.; (ii) H₂SO₄ (conc.); i: RX, NaOH, r.t.

Experimental

General

Melting points were measured with a Buchi melting point apparatus and are uncorrected. TLC was performed on Merck 60 F254 silica gel-coated aluminum sheets and spots were detected by UV light (254 nm). The ¹H-NMR spectra were recorded on a Varian MERCURY-PLUS 400 instrument using the indicated solvents and TMS as an internal standard. MS spectra were recorded on a Hewlett-Packard 5988A instrument. Elemental analyses were performed on a Vario El III CHNS instrument. All solvents and materials were reagent grade and purified as required. 2-Thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**) was prepared as described in our published procedure [5].

4-Amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazol-5-thiol (2)

Method A: To a solution of potassium hydroxide (5.0 g, 0.09 mol) and 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**, 15.1 g, 0.06 mol) in ethanol (450 mL), carbon disulfide (10 mL, 0.16 mol) was added dropwise over a period of half hour at room temperature. The resulting mixture was stirred for 10 hours at room temperature and the precipitate formed was collected by filtration. After washing with ethanol and ethyl ether, the salt formed was dissolved in a solution of ethanol (300 mL) and hydrazine hydrate (85%, 15 mL, 0.26 mol), and then refluxed for 4 hours. After cooling, the mixture was filtered and the filtrate was poured into water (100 mL), acidified with HCl, and the precipitate thus formed was filtered off and crystallized from ethanol to give pure product **2** as a white solid in 38% yield, m.p. 228~229 °C. ¹H-NMR δ (DMSO-d₆): 2.56 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 4.56 (s, 2H, SCH₂), 5.66 (s, 2H, NH₂), 7.12 (s, 1H, CH), 13.67 (s, 1H, SH); Anal. calcd. for C₁₀H₁₂N₈S₂ (308.37): C, 38.96; H, 3.90; N, 36.36. Found: C, 38.69; H, 3.77; N, 36.52.

Method B: Compound **5** (0.01 mol, 2.94 g), prepared as indicated below, was refluxed with an equimolar amount of 80% hydrazine hydrate in methanol (25 mL) for 2 hours. The solution was partially concentrated and cooled and the precipitate formed was filtered off and recrystallized from ethanol, yield: 27%.

5-Alkylthio-4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazoles 3a~c

A mixture of RX (5.6 mmol) and methanol (or DMF, 5 mL) was added dropwise to a stirred solution of compound **2** (1.6 g, 5.0 mmol) and sodium hydroxide (0.2 g, 5.6 mmol) in water (15 mL). The resulting mixture was stirred at room temperature for 2 hours. The precipitate formed was filtered off and recrystallized from ethanol to give the pure title compounds in good yields.

3a: (R = C₆H₅CH₂): m.p. 114~115 °C; yield 82%; ¹H-NMR δ(CDCl₃): 2.60 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 4.29(s, 2H, SCH₂), 4.55(s, 2H, SCH₂), 6.71(s, 2H, NH₂), 7.18(s, 1H, CH), 7.21 (m, 5H, C₆H₅); Anal. calcd. for C₁₇H₁₈N₈S₂ (398.50): C, 51.19; H, 4.52; N, 28.11; Found: C, 51.42; H, 4.37; N, 28.40.

3b: (R = *p*-NO₂C₆H₄CH₂): m.p. 227~228 °C; yield 78%; ¹H-NMR δ (CDCl₃): 2.53 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 4.47 (s, 2H, SCH₂), 4.56 (s, 2H, SCH₂), 6.09 (s, 2H, NH₂), 7.07 (s, 1H, CH), 7.59~8.08 (m, 4H, C₆H₄); Anal. calcd. for C₁₇H₁₇N₉O₂S₂ (443.50): C, 45.99; H, 3.83; N, 28.41; Found: C, 45.67; H, 4.02; N, 28.76.

3c: (R = *p*-ClC₆H₄CH₂): m.p. 175~176 °C; yield 82.5%; ¹H-NMR δ (CDCl₃): 2.62 (s, 3H, CH₃), 2.71 (s, 3H, CH₃), 4.31 (s, 2H, SCH₂), 4.56 (s, 2H, SCH₂), 5.05 (s, 2H, NH₂), 7.07 (s, 1H, CH), 7.19~7.27 (m, 4H, C₆H₄); Anal. calcd. for C₁₇H₁₇N₈ClS₂ (432.94): C, 47.12; H, 3.93; N, 25.87; Found: C, 46.88; H, 3.77; N, 26.24.

3-(5,7-Dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-6-aryl-5,6-dihydrogen-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **4a-c**

The appropriate aryl aldehyde (3.3 mmol) was added to a solution of **2** (1.0 g, 3.3 mmol) and ethanol (60 mL) and the pH value of the mixture was then adjusted to 4~6 with an ethanol solution saturated with HCl gas. The resulting mixture was refluxed for 6~7 hours. After cooling, the precipitate was filtered off and crystallized from DMF/ethanol to give pure products as white solids in excellent yields.

4a (Ar = *p*-CH₃OC₆H₄): m.p. 246~247 °C; yield 80%; ¹H-NMR δ (DMSO-d₆): 2.51 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 4.66 (s, 2H, SCH₂), 7.01 (s, 1H, CH), 6.88~7.65 (m, 4H, C₆H₄), 9.56 (s, 1H, SCH), 13.84(s, 1H, NH); Anal. calcd. for C₁₈H₁₈N₈OS₂ (426.51): C, 50.64; H, 4.22; N, 26.26; Found: C, 50.49; H, 3.97; N, 26.50.

4b (Ar = *p*-CH₃C₆H₄): m.p. 240~241 °C; yield 86%; ¹H-NMR δ (DMSO-d₆): 2.50 (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 2.54 (s, 3H, CH₃), 4.66 (s, 2H, SCH₂), 6.99 (s, 1H, CH), 7.12~7.56 (m, 4H, C₆H₄), 9.69 (s, 1H, SCH), 13.83 (s, 1H, NH); Anal. calcd. for C₁₈H₁₈N₈S₂ (410.51): C, 52.62; H, 4.38; N, 27.28; Found: C, 52.83; H, 4.59; N, 27.61.

4c (Ar = *o*-FC₆H₄): m.p. 237~239 °C; yield 83.7%; ¹H-NMR δ (DMSO-d₆): 2.51 (s, 3H, CH₃), 2.59 (s, 3H, CH₃), 4.70 (s, 2H, SCH₂), 7.02 (s, 1H, CH), 7.15~7.90 (m, 4H, C₆H₄), 10.43 (s, 1H, SCH), 13.91(s, 1H, NH); Anal. calcd. for C₁₇H₁₅N₈FS₂ (414.47): C, 49.22; H, 3.62; N, 27.02; Found: C, 49.50; H, 3.89; N, 27.33.

2-(5,7-Dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,3,4-oxadiazol-5-thiol (**5**)

Compound **1** (5.0 g, 0.02 mol) was added to a solution of KOH (1.3 g, 0.024 mol) in anhydrous EtOH (160 mL). A solution of CS₂ (2.0 g, 0.03 mol) in anhydrous EtOH (40 mL) was then added dropwise to the vigorously stirred mixture, which was refluxed for 6 hours. The solvent was removed under reduced pressure and the residue was dissolved in water (100 mL). After acidification to pH 5~6 with glacial acetic acid the crude product was isolated by filtration and recrystallized from ethanol/petroleum ether to afford 5.5 g of pure **5** as white crystals; m.p. 203-204 °C; yield: 94%; ¹H-NMR δ (CDCl₃): 2.50 (s, 1H, SH), 2.55 (s, 3H, 5-CH₃), 2.65 (s, 3H, 7-CH₃), 4.65 (s, 2H, SCH₂), 7.15 (s, 1H, 6-H); Anal. calcd. for C₁₀H₁₀N₆OS₂ (294.34): C, 40.82; H, 3.40; N, 28.57; Found: C, 40.67; H, 3.51; N, 28.68.

2-(5,7-Dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-5-alkylthio-1,3,4-oxadiazoles **6a~b**

To a stirred solution of **5** (1.5 g, 5.1 mmol) and sodium hydroxide (0.2 g, 5.6 mmol) in water (15 mL), a mixture of a substituted benzyl chloride (5.6 mmol) and methanol (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2 hours. The precipitate formed was filtered off and recrystallized from petroleum ether/acetone to give **6** in good yields.

6a: (R = *p*-NO₂C₆H₄CH₂): m.p. 132~133 °C; yield 56.3%; ¹H-NMR δ (CDCl₃): 2.58 (s, 3H, 5-CH₃), 2.65 (s, 3H, 7-CH₃), 4.41 (s, 2H, CH₂C₆H₄), 4.64 (s, 2H, SCH₂), 6.72 (s, 1H, 6-H), 7.51-8.08 (q, 4H, Ar-H); MS (*m/z*): 429 (M⁺, 1), 293 (4), 262 (15), 261 (100), 221 (3), 219 (7), 193 (11), 180 (6), 149 (5), 148 (2), 136 (4), 108 (23), 107 (14); Anal. calcd. for C₁₇H₁₅N₇O₃S₂ (429.47): C, 47.55; H, 3.50; N, 22.84; Found: C, 48.34; H, 3.96; N, 22.97.

6b: (R = *o*-ClC₆H₄CH₂): m.p. 133~135 °C; yield 75%; ¹H-NMR δ (CDCl₃): 2.65 (s, 3H, 5-CH₃), 2.72 (s, 3H, 7-CH₃), 4.38 (s, 2H, CH₂C₆H₄), 4.72 (s, 2H, SCH₂), 6.77 (s, 1H, 6-H), 7.23-7.39 (q, 4H, Ar-H); Anal. calcd. for C₁₇H₁₅N₆OClS₂ (418.91): C, 48.69; H, 3.58; N, 20.05; Found: C, 48.81; H, 3.75; N, 20.43.

2-(5,7-Dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-5-phenyl-1,3,4-oxadiazole (7)

A mixture of **1** (1.0g, 4.0 mmol), benzoic acid (0.55 mL, 6 mmol) and POCl₃ (5 mL) was refluxed for 6 hours. After cooling to room temperature, the mixture was poured into crushed ice and filtered. The solid was washed with sodium hydroxide solution (5%) and water (x 3) and recrystallized from EtOH to afford yellow crystals (0.9 g, 66% yield); m.p. 171-173 °C; ¹H-NMR δ (CDCl₃): 2.64 (s, 3H, 5-CH₃), 2.73 (s, 3H, 7-CH₃), 4.82 (s, 2H, SCH₂), 6.76 (s, 1H, 6-H), 7.47-8.01 (m, 5H, Ar-H); Anal. calcd. for C₁₆H₁₄N₆OS: C, 56.80; H, 4.14; N, 24.85; Found: C, 57.13; H, 3.87; N, 24.69.

2-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,3,4-thiadiazol-5-thiol (8)

To a solution of potassium hydroxide (4.68 g, 0.08 mol) and 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**, 15.1 g, 0.09 mol) in ethanol (250 mL), carbon disulfide (10 mL, 0.16 mol) was added dropwise at room temperature over a period of half an hour. The resulting mixture was stirred for 12 hours at room temperature and the precipitate formed was collected by filtration. After washing with ethanol and ethyl ether, the salt formed was added to concentrated H₂SO₄ (90 mL). The mixture was stirred at room temperature for 4 hours, poured into crushed ice (250 g) and the precipitate formed was filtered off and dissolved in NaOH solution (250 mL, 2.4 g). After filtration the filtrate was acidified with HCl, and the precipitate thus formed was filtered off and crystallized from ethanol to give pure **8** as yellow crystals (42%); m.p. 217~219 °C; ¹H-NMR δ (CD₃COCD₃): 2.60 (s, 3H, CH₃), 2.76 (s, 3H, CH₃), 4.67 (s, 2H, SCH₂), 7.09 (s, 1H, CH), 13.89 (s, 1H, SH); Anal. calcd. for C₁₀H₁₀N₆S₃ (310.40): C, 38.66; H, 3.22; N, 27.06; Found: C, 38.43; H, 3.51; N, 27.40.

2-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-5-alkylthio-1,3,4-thiadiazoles 9a-c

To a stirred solution of **8** (1.6 g, 5.1 mmol) and sodium hydroxide (0.2 g, 5.6 mmol) in water (15 mL), a mixture of substituted benzyl chloride (5.1 mmol) in methanol (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2.5 hours. The precipitate formed was filtered off and recrystallized from petroleum ether/acetone to give **9** in fair to good yields.

9a (R = C₆H₅CH₂): m.p. 118~120 °C; yield 86%; ¹H-NMR δ (CDCl₃): 2.65 (s, 3H, CH₃), 2.73 (s, 3H, CH₃), 4.50 (s, 2H, SCH₂), 4.84 (s, 2H, SCH₂), 6.78 (s, 1H, CH), 7.25~7.38 (m, 5H, C₆H₅); MS (*m/z*): 400 (M⁺, 9), 309 (1), 237 (8), 181 (11), 180 (7), 149 (9), 148 (9), 91 (100), 67 (17); Anal. calcd. for C₁₇H₁₆N₆S₃ (400.53): C, 50.93; H, 3.99; N, 17.98; Found: C, 51.17; H, 4.26; N, 27.65.

9b (R = *p*-NO₂C₆H₄CH₂): m.p. 145~146 °C; yield 68%; ¹H-NMR δ (CDCl₃): 2.65 (s, 3H, CH₃), 2.72 (s, 3H, CH₃), 4.56 (s, 2H, SCH₂), 4.83 (s, 2H, SCH₂), 6.78 (s, 1H, CH), 7.56~8.14 (m, 4H, C₆H₄); MS (*m/z*): 446 (M⁺, 7), 309 (10), 237 (25), 219 (12), 149 (26), 148 (20), 136 (15), 107 (60), 46 (24), 32 (100); Anal. calcd. for C₁₇H₁₅N₇O₂S₃ (445.53): C, 45.79; H, 3.37; N, 21.99. Found: C, 45.97; H, 3.65; N, 22.33.

9c (R = *p*-ClC₆H₄CH₂): m.p. 146~147 °C; yield 44%; ¹H-NMR δ (CDCl₃): 2.65 (s, 3H, CH₃), 2.72 (s, 3H, CH₃), 4.45 (s, 2H, SCH₂), 4.84 (s, 2H, SCH₂), 6.78 (s, 1H, CH), 7.24~7.34 (m, 4H, C₆H₄); MS (*m/z*): 435 (M⁺, 7), 309 (4), 237 (10), 193 (3), 181 (19), 125 (100), 108 (14), 107 (25); Anal. calcd. for C₁₇H₁₅N₆ClS₃ (434.97): C, 46.89; H, 3.45; N, 19.31; Found: C, 46.61; H, 3.23; N, 19.64.

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Sample Availability: Samples of the compounds are available from the authors.

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