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[a] Center for Instrumental Analysis, Iwate University, Morioka, Iwate, Japan [b] Department of Chemical Engineering, Faculty of Engineering, Iwate University, Morioka, Iwate, Japan

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Preparation of pentathiepinoquinoline via ipso-substitution reactions of phenylsulfinyl and *iso*-propylsulfinyl groups with sulfur anions in liquid ammonia

Takeshi Kimura[a]*, Nobuyuki Takahashi[b], Masato Sasage[b], Toshiharu Namauo[a], Satoshi Ogawa[b] and Ryu Sato[b]

[a]*Center for Instrumental Analysis, Iwate University, Morioka, Iwate 020-8551, Japan;* [b]*Department of Chemical Engineering, Faculty of Engineering, Iwate University, Morioka, Iwate 020-8551, Japan*

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This paper is dedicated to Professor Juzo Nakayama on the occasion of his 65th birthday and retirement.

3-Phenylsulfinyl-4-isopropylsulfinylquinolines (**5a**,**b**) were prepared from 3-bromoquinoline via four-step reactions. Compounds (**5a**,**b**) were treated with elemental sulfur in liquid ammonia at 120 °C for 12 h. The reaction mixture was cooled and dropped into dichloromethane and stirred for 24 h. After purification of the product, pentathiepinoquinoline (**6**) was obtained in low yield.

Keywords: pentathiepin; quinoline; sulfur heterocycles; liquid ammonia

1. Introduction

Benzo[1,2,3,4,5]pentathiepin and related compounds are interesting molecules due to their structure, reactivity, electrochemical properties, and biological activities (*1–2*). *Varacin* and *Lissoclinotoxin A* are the first benzo[1,2,3,4,5]pentathiepins obtained from marine ascidian that exhibit antitumor and antifungal activities (Figure 1) (*3*). It is expected that the aminoethyl group next to the pentathiepin ring cleaves the sulfur linkage of the pentathiepin ring, which is important for antitumor activity (*4*). Heterocyclic compounds fused with the pentathiepin ring could be interesting for their biological activities. Until now, it has been reported that thiazolopentathiepin, pyrazolopentathiepin, pentathiepinoindole, and related derivatives were prepared, and that some of them have antifungal activities (*5–9*). For preparation of pentathiepin derivatives fused with heterocycles, a procedure that can easily be applied to introduce sulfur functional groups on the desired ring systems is required. On the other hand, we have continuously studied benzo-annelated cyclic oligosulfides (*10–13*). An important result is the preparation of

*Corresponding author. Email: kimura@iwate-u.ac.jp

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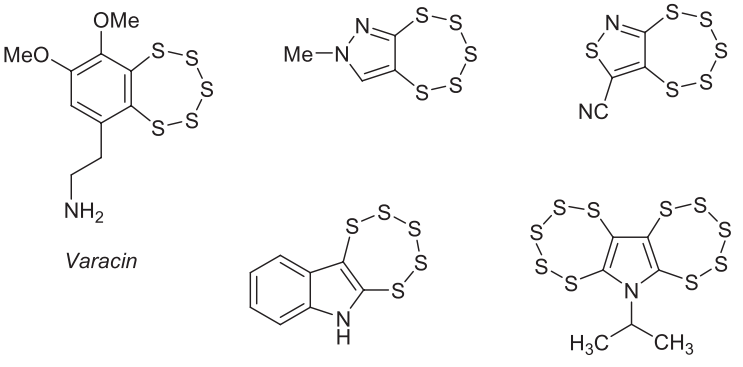


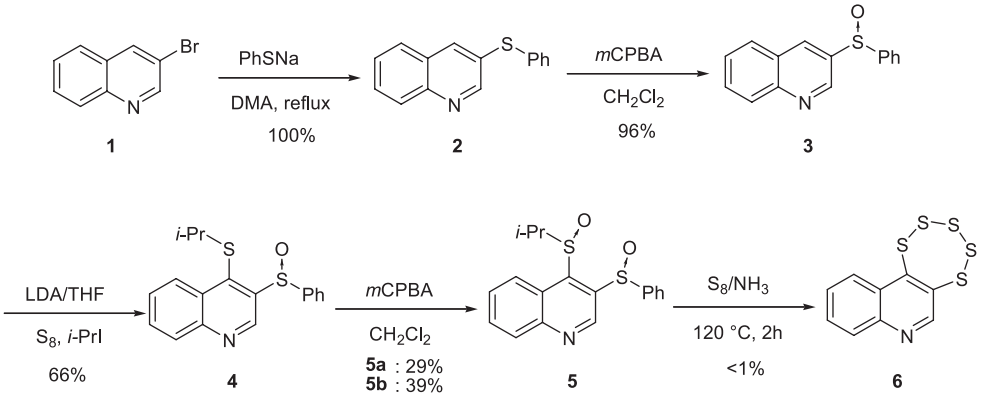
Figure 1. Varacin and pentathiepinoheterocycles.

6,10-diethyl[1,2,3]trithiolo[4,5-*h*]benzo[1,2,3,4,5]pentathiepin and 4,8-diethylbenzo[1,2-d:4,5-d']bis[1,2,3]trithiole by the reaction of 2,3,5,6-tetrabromo-1,4-diethylbenzene with elemental sulfur in liquid ammonia at 120 °C (*11*). The reaction is a method to introduce sulfur functional groups on the benzene ring by the ipso-substitution reaction (*14*). In the course of our studies with respect to benzo-annelated cyclic oligosulfides, we were interested in the preparation of molecules that consisted of the pentathiepin and pyridine or quinoline rings. In this paper, the preparation of pentathiepinoquinoline (**6**) from 3-phenylsulfinyl-4-isopropylsulfinylquinoline (**5a**,**b**) by the ipso-substitution reaction of two sulfinyl groups with elemental sulfur in liquid ammonia is described.

2. Results and discussion

Stabilizing the oligosulfide ring fused to the benzene ring frequently requires that the molecule has one or two substituents next to the sulfur linkage (*1, 2*). Therefore, we selected the quinoline ring as a heterocycle because if the oligosulfide ring can be constructed at the 3,4-positions of quinoline, the benzene ring is expected to act as a close substituent. There are several reports regarding the preparation of quinoline derivatives with sulfur functional groups (*15*). Although the products in these reports are thioquinanthrene and isothioquinanthrene, it seemed that functionalization with sulfur substituents would be easily performed at the 3,4-positions of quinoline. To introduce a sulfur functional group and to avoid dimerization of quinoline, 3-bromoquinoline (**1**) was selected and treated with sodium thiophenolate in DMA at reflux temperature for 24 h to produce 3-phenylthioquinoline (**2**) in quantitative yield (Scheme 1) (*16*).

It was reported that the reaction of pyridyl phenyl sulfoxide with alkyl lithium or Grignard reagents produced functionalized pyridine derivatives (*17*). The oxidation of **2** with *m*CPBA in dichloromethane at room temperature produced 3-phenylsulfinylquinoline (**3**) in 96% yield. Compound (**3**) was treated with lithium diisopropyl amide (LDA) in THF at −78 °C and then with elemental sulfur and isopropyl iodide at room temperature to give 3-phenylsulfinyl-4-isopropylthioquinoline (**4**) in 66% yield. It was reported that the bromine atoms of tetrabromo-1,4-diethylbenzene were substituted with elemental sulfur in liquid ammonia or DBU at 120 °C (*11,14*). It is expected that the sulfinyl and sulfonyl groups could be substituted with sulfurization reagents in liquid ammonia. Compound (**4**) was then oxidized by *m*CPBA to produce 3-phenylsulfinyl-4-isopropylsulfinylquinoline (**5**) as a diastereomeric mixture (68%, **5a** : **5b** = 2 : 3).

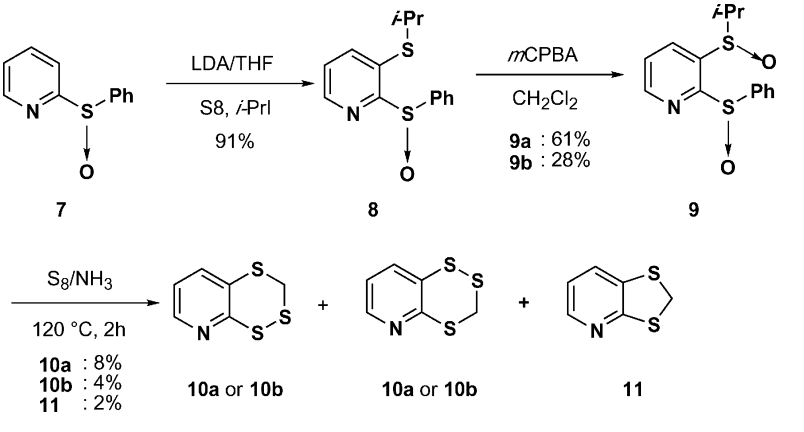


Scheme 1.

Constructing the pentathiepin ring on the quinoline ring was tried upon treatment of **5a**,**b** with elemental sulfur in liquid ammonia at 120 °C for 12 h. After cooling, the reaction mixture was dropped into dichloromethane through a needle valve and the solution was stirred for 24 h. The solvent was evaporated and the residue was purified, giving a pale yellow product in low yield (<1%). In the ^{1}H NMR spectrum, disappearance of the isopropyl and phenyl groups and signals of the quinoline ring could be observed. Mass spectrum analysis showed the molecular ion peak of pentathiepinoquinoline (**6**) at $m/z = 287$. It appeared that two sulfinyl groups were substituted with sulfur anions under the reaction conditions to construct the pentathiepin rings. Finally, elemental analysis of **6** was performed, which supports the structure of **6**. Compound (**6**) was stable at ambient temperature under air.

Since the quinoline derivative (**6**) was obtained as described above, we then attempted to prepare pyrido[1,2,3,4,5]pentathiepin and to assess the effect of the benzene ring fused to **6**. To introduce the pentathiepin ring on the pyridine ring, 2-pyridyl phenyl sulfoxide (**7**) was selected as a starting material. By a procedure similar to that described above, 2-phenylsulfinyl-3-isopropylsulfinylpyridine (**9a**,**b**) was obtained as a mixture of two diastereomeric isomers by way of 2-phenylsulfinyl-3-isopropylthiopyridine (**8**) (Scheme 2).

Compounds (**9a**,**b**) were reacted with elemental sulfur in liquid ammonia at 120 °C for 12 h. After cooling, the reaction mixture was dropped into dibromomethane and the solution was stirred for 24 h.[1] The solvent was evaporated and the residue was purified, giving three pale yellow



Scheme 2.

compounds (**10a**), (**10b**), and (**11**) in low yields. In the ^{1}H NMR spectrum of **11**, disappearance of the isopropyl and phenyl groups, three signals for the pyridine ring, and one signal for the methylene group, could be observed. The integral ratio of the methylene signal, newly appeared, and the signals of the pyridine ring, were 2:1:1:1. Mass spectrum analysis showed the molecular ion peak at $m/z = 156$ [MH$^+$]. Based on the spectroscopic results, the product was expected to be pyrido[1,3]dithiole (2%). In contrast, the ^{1}H NMR spectra of **10a** and **10b** showed disappearance of the isopropyl and phenyl groups and four signals for the pyridine ring (three protons) and the methylene group (two protons). In the mass spectra, the molecular ion peaks of **10a** and **10b** were observed as the same signal at $m/z = 187$ [M$^+$]. These results suggested that compounds **10a** (8%) and **10b** (4%) were pyrido[1,2,4]trithiin and pyrido[1,3,4]trithiin. However, we could not determine which structures corresponded to **10a** and **10b**. It appeared that the methylene group originates from dibromomethane. On the other hand, pyrido[1,2,3,4,5]pentathiepin and other cyclic oligosulfides could not be observed in the reaction products, though dichloromethane was used as the solvent.[1] The oligosulfide ring constructed on the pyridine ring should be unstable when the sulfur ring contains a trisulfide or longer sulfur linkage.

3. Conclusion

The substitution reactions of the phenylsulfinyl and isopropylsulfinyl groups on the quinoline or pyridine ring with the generated sulfurization reagent proceeded under the reaction conditions to give pentathiepinoquinoline (**6**) or pyridotrithiins (**10a**,**b**). The reaction could be the ipso-substitution with the sulfur anions while generation of pyridyne derivatives and their addition reaction with elemental sulfur might be possible. Pyridopentathiepin could not be obtained by this treatment, suggesting that the benzene ring of quinoline in the molecule (**6**) is important in stabilizing the pentathiepin ring.

4. Experimental

4.1. *General*

The NMR spectra were measured on a Bruker AC-400 spectrometer. The IR spectra were recorded using a JASCO FT-7300 spectrometer. The mass spectra were obtained using a Hitachi M-2000 mass spectrometer and a JEOL MS-700 mass spectrometer. Elemental analyses were performed using a Yanako MT-5 analyzer.

4.2. *Preparation of 3-phenylthioquinoline (2)*

To a solution of thiophenol (20.5 ml, 200 mmol) in DMA (100 ml), sodium ethoxide (6.8 g, 200 mmol) in 100 ml ethanol was added and the resulting solution was stirred for 2 h at room temperature. To the solution, 3-bromoquinoline (**1**) (13.46 g, 100 mmol) in DMA (100 ml) was added and the resulting solution was refluxed for 24 h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CCl_4–CH_2Cl_2) to produce compound (**2**) in 100% yield (23.638 g); colorless needle; mp 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.36 (m, 3H, PhH), 7.38–7.41 (m, 2H, PhH), 7.54 (dt, $J = 7.8$, 1.1 Hz, 1H, ArH), 7.69 (dt, $J = 7.8$, 1.1 Hz, 1H, ArH), 7.70 (dd, $J = 7.8$, 1.1 Hz, 1H, ArH), 8.07 (d, $J = 2.2$ Hz, 1H, ArH), 8.08 (dd, $J = 7.8$, 1.1 Hz, 1H, ArH), 8.81 (d, $J = 2.2$ Hz, 1H, ArH); MS (m/z) 237 (M$^+$); Anal. Calcd for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.90%. Found: C, 76.00; H, 4.50; N, 5.81%.

4.3. *Oxidation of (2) with mCPBA*

To a solution of **2** (9.619 g, 40.5 mmol) dissolved in CH_2Cl_2 (100 ml), a solution of *m*CPBA (9.98 g, 40.5 mmol, assay ≥70%) in CH_2Cl_2 (200 ml) was slowly added and the resulting solution was stirred at room temperature for 10 h. After treatment with NH_3, the solution was filtered under reduced pressure. The filtrate was evaporated and the products were purified by column chromatography (silica gel; hexane : AcOEt = 3 : 1) to give 3-phenylsulfinylquinoline (**3**) in 96% (9.8 g); colorless needles; mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.52 (m, 3H, PhH), 7.64 (dt, J = 8.3, 1.2 Hz, 1H, ArH), 7.71–7.74 (m, 2H, PhH), 7.80 (dt, J = 8.3, 1.2 Hz, 1H, ArH), 7.93 (dd, J = 8.3, 1.2 Hz, 1H, ArH), 8.12 (dd, J = 8.3, 1.2 Hz, 1H, ArH), 8.61 (d, J = 2.1 Hz, 1H, ArH), 8.88 (d, J = 2.1 Hz, 1H, ArH); IR (KBr) 1046 cm^{-1} (SO); MS (m/z) 253 (M^+); Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53%. Found: C, 71.43; H, 4.19; N, 5.41%.

4.4. *Preparation of 3-phenylsulfinyl-4-isopropylthioquinoline (4)*

Compound (**3**) (390 mg, 1.5 mmol) dissolved in THF (30 ml) was lithiated with 0.136 M LDA (22 ml, 3 mmol) at −78 °C for 1 h under Ar. Elemental sulfur (241 mg, 7.5 mmol) was then added. After the mixture was stirred for 2 h at room temperature, isopropyl iodide (0.56 ml, 9 mmol) was added and the resulting solution was stirred for another 12 h. The solution was treated with water and the solvent was evaporated. Saturated NH_4Cl solution (100 ml) was added and the solution was extracted with CH_2Cl_2 (100 ml × 3). The solvent was evaporated and the product was purified by column chromatography (silica gel, hexane : AcOEt = 2 : 1) to produce **4** in 65% yield (320 mg); colorless needles; mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.8 Hz, 3H, CH_3), 1.33 (d, J = 6.8 Hz, 3H, CH_3), 3.60 (sept, J = 6.8 Hz, 1H, CH), 7.40–7.46 (m, 3H, PhH), 7.67 (dt, J = 8.3, 1.2 Hz, 1H, ArH), 7.80 (dt, J = 8.3, 1.2 Hz, 1H, ArH), 7.84–7.86 (m, 2H, PhH), 8.16 (dd, J = 8.3, 1.2 Hz, 1H, ArH), 8.49 (dd, J = 8.2, 1.2 Hz, 1H, ArH), 9.37 (s, 1H, ArH); IR (KBr) 1049 cm^{-1} (SO); MS (m/z) 327 (M^+); Anal. Calcd for $C_{18}H_{17}NOS_2$: C, 66.02; H, 5.23; N, 4.28%. Found: C, 66.17; H, 5.12; N, 4.08%.

4.5. *Oxidation of (4) with mCPBA*

To a solution of **4** (654 mg, 2 mmol) dissolved in 100 ml of CH_2Cl_2, a solution of *m*CPBA (343 mg, 2 mmol, assay ≥99%) in CH_2Cl_2 (100 ml) was slowly added and the resulting solution was stirred at room temperature for 10 h. After treatment with NH_3, the solution was filtered under reduced pressure. The filtrate was washed with aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (50 ml × 3). The solvent was evaporated and the products were purified by column chromatography (silica gel; hexane : AcOEt = 1 : 1) to give a diastereomeric mixture of 3-phenylsulfinylquinoline (**5a,b**) in 68% yield (461 mg). The ratio of **5a** to **5b** was determined with ^{1}H NMR as 2:3. Compounds **5a** and **5b** could be separated from each other by column chromatography; **5a**: pale yellow crystals; mp 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.4 Hz, 3H, CH_3), 1.47 (d, J = 6.4 Hz, 3H, CH_3), 3.75 (sept, J = 6.4 Hz, 1H, CH), 7.45–7.56 (m, 3H, PhH), 7.68 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H, ArH), 7.83–7.91 (m, 2H, PhH, ArH), 8.22 (d, J = 8.4 Hz, 1H, ArH), 9.04 (br, 1H, ArH), 9.43 (2, 1H, ArH); IR (KBr) 1064, 1024 cm^{-1} (SO); MS (m/z) 343 (M^+); Anal. Calcd for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08%. Found: C, 62.81; H, 5.05; N, 3.79%; **5b**: pale yellow crystals; mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.8 Hz, 3H, CH_3), 1.62 (d, J = 6.8 Hz, 3H, CH_3), 3.79 (sept, J = 6.8 Hz, 1H, CH), 7.38–7.49 (m, 3H, PhH), 7.68 (dd, J = 8.3 Hz, 1H, ArH), 7.86 (dt, J = 8.3, 1.1 Hz, 1H, ArH), 7.99 (d, J = 7.5 Hz, 2H, PhH), 8.09–8.19 (m, 1H, ArH), 8.20

(d, $J = 8.3$ Hz, 1H, ArH), 9.62 (s, 1H, ArH); IR (KBr) 1067, 1042, 1029 cm^{-1} (SO); MS (m/z) 343 (M^+); Anal. Calcd for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08%. Found: C, 62.79; H, 4.91; N, 3.86%.

4.6. *Treatment of (5) with S_8/NH_3 at 120 °C*

Compound (**5**) (172 mg, 0.5 mmol) was reacted with elemental sulfur (401 mg, 12.5 mmol)/NH_3 (30 ml) in an autoclave at 120 °C for 12 h. After cooling, the reaction mixture was dropped into CH_2Cl_2 (200 ml) and the resulting solution was stirred at room temperature for 12 h. After filtration and evaporation of the solvent, the products were purified by column chromatography (silica gel; hexane and then hexane : AcOEt = 10 : 1) to give **6** in low yield (<1%); pale yellow crystals; mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, $J = 8.3$ Hz, 1H, ArH), 7.84 (t, $J = 8.3$ Hz, 1H, ArH), 8.19 (d, $J = 8.3$ Hz, 1H, ArH), 8.59 (d, $J = 8.3$ Hz, 1H, ArH), 9.27 (s, 1H, ArH); MS (m/z) 287 (M^+); Anal. calcd for $C_9H_5NS_5$: C, 37.61; H, 1.75; N, 4.87%. Found: C, 37.54; H, 1.99; N, 4.73%.

4.7. *Preparation of 2-phenylsulfinyl-3-isopropylthiopyridine (8)*

To a solution of compound (**7**) (2.033 g, 10 mmol) dissolved in THF (30 ml), 0.381 M LDA (39.6 ml, 15.1 mmol) was added at −78 °C and the resulting solution was stirred for 45 h under Ar. Elemental sulfur (1.604 g, 50 mmol) was then added. After the mixture was stirred for 5 h at room temperature, isopropyl iodide (9.9 ml, 100 mmol) was added and the solution was stirred for another 12 h. The solution was treated with water and $NaHCO_3$ solution (1 M, 100 ml) was added. The solution was extracted with CH_2Cl_2 (100 ml × 3) and the solvent was evaporated. The product was purified by column chromatography (silica gel, hexane : AcOEt = 3 : 1 and MeOH) to produce **8** in 91% yield (2.526 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, $J = 6.6$ Hz, 3H, CH_3), 1.33 (d, $J = 6.6$ Hz, 3H, CH_3), 3.40 (sept, $J = 6.6$ Hz, 1H, CH), 7.31 (dd, $J = 7.8$, 4.6 Hz, 1H, ArH), 7.40–7.45 (m, 3H, PhH), 7.73 (dd, $J = 7.8$, 1.5 Hz, 1H, ArH), 7.85–7.90 (m, 2H, PhH), 8.66 (dd, $J = 4.6$, 1.5 Hz, 1H, ArH); IR (KBr) 1047 cm^{-1} (SO); HRMS calcd for $C_{14}H_{15}NO_2S_2$, 277.0595. Found (m/z) 277.0598 (M^+).

4.8. *Preparation of 2-phenylsulfinyl-3-isopropylsulfinylpyridine (9)*

To a solution of **8** (619 mg, 2.41 mmol) dissolved in CH_2Cl_2 (100 ml), a solution of *m*CPBA (477 mg, 2.49 mmol, assay ≥90%) in CH_2Cl_2 (100 ml) was added and the resulting solution was stirred at room temperature for 4 h. After treatment with NH_3, the solution was washed with $NaHCO_3$ solution (1 M, 100 ml). The solution was dried and evaporated and the products were purified by column chromatography (silica gel; hexane : AcOEt = 3 : 1) to give **9a** in 61% (442 mg) and **9b** in 28% (201 mg) yield; **9a**: colorless crystals; mp 106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, $J = 6.9$ Hz, 3H, CH_3), 1.55 (d, $J = 6.9$ Hz, 3H, CH_3), 3.41 (sept, $J = 6.9$ Hz, 1H, CH), 7.49–7.53 (m, 3H, PhH), 7.55 (dd, $J = 7.9$, 4.6 Hz, 1H, ArH), 7.82–7.84 (m, 2H, PhH), 8.44 (dd, $J = 7.9$, 1.6 Hz, 1H, ArH), 8.67 (dd, J = 4.6, 1.6 Hz, 1H, ArH); IR (KBr) 1047, 1024 cm^{-1} (SO); **9b**: colorless crystals; mp 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, $J = 6.9$ Hz, 3H, CH_3), 1.56 (d, $J = 6.9$ Hz, 3H, CH_3), 3.67 (sept, $J = 6.9$ Hz, 1H, CH), 7.45–7.48 (m, 3H, PhH), 7.50 (dd, $J = 7.9$, 4.6 Hz, 1H, ArH), 7.85–7.88 (m, 2H, PhH), 8.45 (dd, $J = 7.9$, 1.6 Hz, 1H, ArH), 8.59 (dd, $J = 4.6$, 1.6 Hz, 1H, ArH); IR (KBr) 1049, 1025 cm^{-1} (SO); HRMS calcd for $C_{14}H_{15}NO_2S_2$, 293.0544. Found (m/z) 293.0543 (M^+).

4.9. *Treatment of (9) with S_8/NH_3 at 120 °C*

Compound (**9**) (0.294 mg, 0.5 mmol) was reacted with elemental sulfur (802 mg, 25 mmol)/NH_3 (30 ml) in an autoclave at 120 °C for 12 h. After cooling, the reaction mixture was dropped into CH_2Br_2 (200 ml) and the resulting solution was stirred at room temperature for 12 h. After filtration and evaporation of the solvent, the products were purified by column chromatography (silica gel; hexane and then hexane : AcOEt = 10 : 1) to give **10**a (6%), **10b** (3%), and **11** (2%); **10a**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H, CH_2), 7.00 (dd, $J = 7.8$, 4.6 Hz, 1H, ArH), 7.58 (dd, $J = 7.8$, 1.6 Hz, 1H, ArH), 8.33 (dd, $J = 4.7$, 1.6 Hz, 1H, ArH); MS (m/z) 187 (M^+); **10b**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2H, CH_2), 7.09 (dd, $J = 7.8$, 4.9 Hz, 1H, ArH), 7.40 (dd, $J = 7.8$, 1.1 Hz, 1H, ArH), 8.07 (dd, $J = 4.6$, 1.1 Hz, 1H, ArH); MS (m/z) 187 (M^+); **11**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2H, CH_2), 7.09 (dd, $J = 8.0$, 4.6 Hz, 1H, ArH), 7.55 (dd, $J = 8.0$, 1.7 Hz, 1H, ArH), 8.25 (dd, $J = 4.6$, 1.7 Hz, 1H, ArH); MS (m/z) 156 (MH^+).

Note

1. When dichloromethane was used as the solvent, a mixture of **10a** and **10b** was obtained in low yield.

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