On the Syntheses of 1,3-Disubstituted Dithieno[3,4-*b*:3',2'-*d*]pyridines *via* Halogen-metal Exchange of 1,3-Dibromodithieno[3,4-*b*:3',2'-*d*]pyridine

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Halogen-metal exchange of 1,3-dibromodithieno[3,4-*b*:3',2'-*d*]pyridine with butyllithium under different conditions has been studied. Upon reaction with iodine, *N,N*-dimethylacetamide, *N,N*-dimethylformamide, dimethyl carbonate, dimethyl disulfide and thiuram disulfide, the 1,3-diiodo-, 1,3-diacetyl-, 1,3-diformyl-, 1,3-dicarbomethoxy, 1,3-di(thiomethyl)- and 1,3-di(*N,N*-dimethyldithiocarbamoyl)dithieno[3,4-*b*:3',2'-*d*]-pyridines, respectively, were obtained in varying yields. 3-Monosubstituted derivatives were obtained in some cases. The formation of 3,7-disubstituted derivatives was sometimes also observed.

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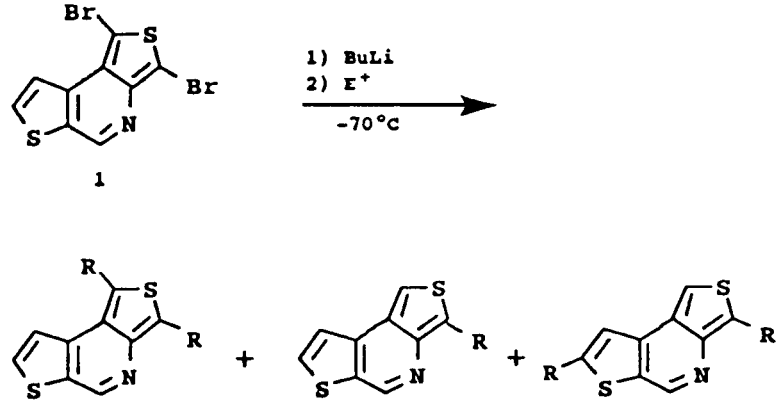
Introduction.

In connection with our interest in the effect of the mode of annelation on reactivity and orientation in dithieno-[*b,d*]pyridines, we have previously studied nitration [1-3], metalation [4,5] and bromination [5,6] of several dithieno[*b,d*]pyridines. One equivalent of bromine gave a mixture of mainly starting material and disubstituted products and only small amounts of monobromo derivatives [5,6] were obtained. However, using two equivalents of bromine gave good yields of 1,3-dibromodithieno[3,4-*b*:3',2'-*d*]pyridine (**1**) [5] and 1,2-dibromo[2,3-*b*:3',2'-*d*]-pyridine [6] from the corresponding parent compounds. Compounds like **1** appear to be promising starting materials for various 1,3-disubstituted derivatives of pharmacological interest, through halogen-metal exchange followed by reaction with various electrophiles.

Halogen-metal exchange between **1** and butyllithium was carried out at -70° in anhydrous ether and in tetrahydrofuran, and the 1,3-dilithium derivative reacted with various electrophiles, such as the carbonyl derivatives *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl carbonate and methyl chloroformate, sulfur-containing electrophiles such as dimethyl disulfide and tetramethylthiuram disulfide, and with iodine (Scheme 1). The yields of 1,3-disubstituted derivatives was somewhat higher in tetrahydrofuran than in ether, and in addition by-products consisting of 3-monosubstituted derivatives were formed in smaller amounts than in ether, where normally about 15% of these derivatives were obtained (*cf* Table 1). With tetramethyl thiuram disulfide, the 3-monosubstituted



R = SCH_3	2		
R = I	3	4	
R = $COCH_3$	5	6	
R = CHO	7	8	9
R = $SCSN(CH_3)_2$	10	11	12

Scheme 1

derivative **11** was even the main product. The reason for the formation of monosubstituted products is not obvious. We know that dilithiation is complete after about 15 minutes at -70°, as upon hydrolysis only the parent compound is formed and no monobromo derivatives could be detected. It could be that the second mole of the electrophile reacts more slowly, so that complete conversion was not obtained.

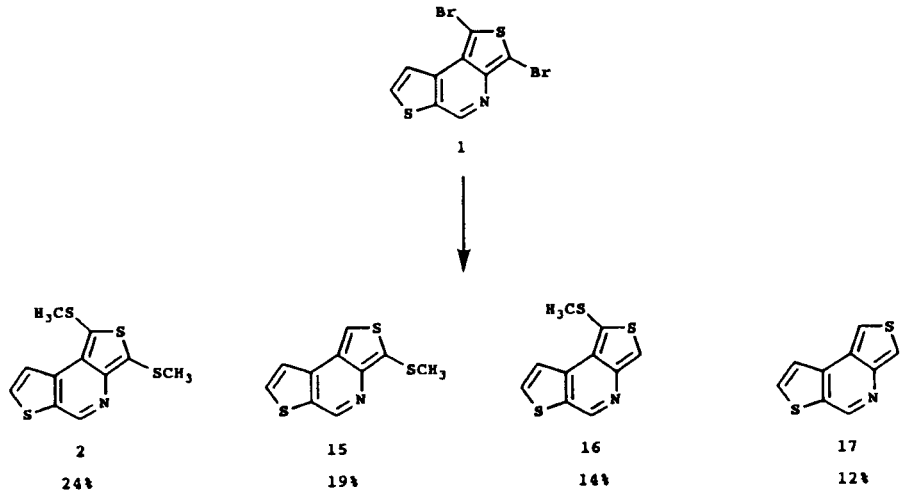
Alternatively, accidental hydrolysis of an intermediate monolithium derivative could lead to the 3-substituted product. In order to find out if the two non-equivalent lithium substituents had different reactivities towards electrophiles, the 1,3-dilithio derivative was reacted with only one equivalent of dimethyl disulfide, followed by hydrolysis. As can be seen from Scheme 2, 24% of **2**, 19% of the 3-methylthio derivative **15**, 14% of the 1-methylthio derivative **16** and 12% of the debrominated compound **17** were obtained, thus eliminating the possibility of selective reaction of the 1-lithium of the 1,3-dilithio derivative. Compounds **15** and **16** could be isolated in pure form by chromatography.

Table 1

Yields in Diethyl Ether (DEE) and Tetrahydrofuran (THF) for some Substituted Dithieno[3,4-*b*:3',2'-*d*]pyridines

Substituent	Compound	Yield (%) DEE	THF
SCH_3	**2**	64	
I	**3**	43	57
	4	12	4
$COCH_3$	**5**	22	41
	6	16	6
CHO	**7**	30	47
	8	12	3
	9		5
$SCSN(CH_3)_2$	**10**	4	28
	11	25	trace
	12		6
$COOCH_3$	**13**		36
	14		4

succeed, since the excess of chloroformate will react with the basic nitrogen [7].



Scheme 2

In the reaction of **1** with two equivalents of butyllithium in tetrahydrofuran followed by *N,N*-dimethylformamide, dimethyl carbonate and tetramethyl thiuram disulfide, 4-6% of the 3,7-disubstituted derivatives were also obtained, probably due to partial transmetallation. In the preparation of the 1,3-dicarbomethoxy derivatives, we obtained much better yields with dimethyl carbonate than with methyl chloroformate. When methyl chloroformate was used the yield was 20%, even though it is said that reactions of chloroformates with lithium derivatives of heterocycles containing an azomethine function cannot

EXPERIMENTAL

The reactions were carried out in dried glassware equipped with tight-fitting septa and under a positive pressure of dry nitrogen. Reagents and solvents were handled by using standard syringe techniques. The ir spectra were recorded on a Perkin Elmer 298 spectrometer. The ^1H nmr spectra were recorded on a Varian XL 300 spectrometer using deuteriochloroform as solvent. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. The elemental analyses were carried out by Dornis and Kolbe, Miroanalytisches Laboratorium, Mulheim a. d. Ruhr, Germany. All melting points are uncorrected. Flash column

chromatography was carried out using Merck silica gel 60. For hplc a preparative polygosil/silica column (250 x 20 mm) was used. Anhydrous reagents and solvents were used. Diethyl ether and tetrahydrofuran were freshly distilled from sodium dispersion. Dichloromethane, petroleum ether, pentane and ethyl acetate were distilled over molecular sieves, and chloroform was distilled over phosphorous pentoxide prior to use.

Di-1,3-(thiomethyl)dithieno[3,4-b:3',2'-*d*]pyridine (**2**).

A 250 ml three-necked flask was charged with 349 mg (1.00 mmole) of sublimed 1,3-dibromodithieno[3,4-*b*:3',2'-*d*]pyridine (**1**) [5] in 100 ml of anhydrous ether. At -70° 1.10 ml (2.20 mmoles) of 2.0*N* butyllithium in cyclohexane diluted with 10 ml of anhydrous ether was added dropwise under nitrogen with stirring. When the addition was complete, the stirring was continued for an additional 15 minutes, after which 0.20 ml (2.20 mmoles) of freshly distilled dimethyl disulfide in 10 ml of anhydrous ether was added dropwise. After 2 hours at -70°, and 1 hour at -30°, the reaction mixture was allowed to reach 0° and treated with ice and 1*N* hydrochloric acid with stirring. The stirring was continued for half an hour at room temperature, whereupon the phases were separated. The water phase was neutralized with saturated sodium hydrogen carbonate solution and extracted three times with ether. The combined organic phases were washed with ice-cooled water, treated with charcoal, dried over magnesium sulfate and evaporated. The residue was chromatographed using ethyl acetate/petroleum ether (1:10) and (1:3) as eluents; 181 mg (64%) of **2** was obtained as a yellow solid substance, which after sublimation at 58°/0.8 mm Hg had mp 81.5-83.5°; ^{1}H nmr: δ 8.98 (d, 1H, 5-H, J = 0.76 Hz), 8.54 (dd, 1H, 8-H, J = 5.28, 0.76 Hz), 7.82 (d, 1H, 7-H, J = 5.28 Hz), 2.65 (s, 3H, SCH_3), 2.53 (s, 3H, SCH_3)

Anal. Calcd. for $C_{11}H_9NS_4$: C, 46.60; H, 3.20; N, 4.94; MW 283.47. Found: C, 46.70; H, 3.26, N, 4.88; MW 283.

1,3-Diiododithieno[3,4-*b*:3',2'-*d*]pyridine (**3**).

A three-necked 250 ml flask was flushed with nitrogen and charged with 698 mg (2.00 mmoles) of sublimed **1** in 40 ml of anhydrous tetrahydrofuran. At -70°, 2.20 ml of 2.0*N* butyllithium in cyclohexane diluted with 10 ml of anhydrous tetrahydrofuran was added dropwise with stirring under nitrogen. After 15 minutes of additional stirring, 1.12 g (4.40 mmoles) of iodine in 30 ml of anhydrous tetrahydrofuran was added dropwise. The reaction mixture was kept at -70° for 2-3 hours and at -30° for 1 hour, and at 0° it was poured into ice and treated with a mixture of 1*N* hydrochloric acid and dichloromethane (1:1) with stirring. The stirring was continued for half an hour and the phases were separated. The water phase was neutralized with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic phases were washed with sodium hydrogen sulfite solution (10%), 2*N* sodium hydroxide solution, and ice-water, treated with charcoal and dried over magnesium sulfate. After evaporation the residue was chromatographed using ethyl acetate/petroleum ether (1:10) and chloroform/pentane (1:1) as eluents. 505 mg (57%) of **3** was obtained as a yellow solid substance, which after sublimation at 122°/0.8 mm Hg had a mp 154.5-156.0°. When **3** was prepared in analogy with **2**, the yield was 191 mg (43%); ^{1}H nmr: δ 8.98 (d, 1H, 5-H, J = 0.78 Hz), 8.74 (dd, 1H, 8-H, J = 5.29, 0.78 Hz), 7.88 (d, 1H, 7-H, J = 5.29 Hz).

Anal. Calcd. for $C_9H_3I_2NS_2$ C, 24.39; H, 0.68; N, 3.16; MW 443.10. Found: C, 24.28; H, 0.76; N, 3.16; MW 443.

3-Iododithieno[3,4-*b*:3',2'-*d*]pyridine (**4**).

The later fractions from the chromatography described above were concentrated, and separated by hplc using dichloromethane/ethyl acetate (98:2) as eluent. 26 mg (4%) of 4 was obtained as yellow crystals, which after sublimation at 136°/1 mm Hg had a mp of 160.0-161.5°. When the procedure for the preparation of **2** was used the yield was 38 mg (12%); ^{1}H nmr: δ 9.03 (d, 1H, 5-H, J = 0.79 Hz), 8.13 (s, 1H, 1-H), 7.83 (dd, 1H, 8-H, J = 5.18, 0.79 Hz), 7.72 (d, 1H, 7-H, J = 5.18 Hz).

Calcd. for $C_9H_4INS_2$: 316.8830; hrms Found: 316.8833.

1,3-Diacetyldithieno[3,4-*b*:3',2'-*d*]pyridine (**5**).

This compound was prepared as described for **2** from 349 mg (1.00 mmole) of **1** and 0.47 ml (5.00 mmoles) of freshly distilled *N,N*-dimethylacetamide. After evaporation the residue was chromatographed using ethyl acetate/petroleum ether (1:3) and (1:1) as eluents. 60.0 mg (22%) of **5** was obtained as yellow crystals, which after sublimation at 186°/1 mm Hg and hplc dichloromethane/ethyl acetate (92:2) as eluent had a mp of 220.0-221.0°. When **5** was prepared according to the procedure for **3**, 255.5 mg (41%) was isolated; ir (potassium bromide): ν CO 1635, 1675 cm^{-1}; ^{1}H nmr: δ 9.16 (d, 1H, 5-H, J = 0.81 Hz), 8.27 (br s, 2H, H_7 and H_8), 3.07 (s, 3H, $COCH_3$), 2.76 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{13}H_9NO_2S_2$: C, 56.70; H, 3.29; N, 5.08; MW 275.35. Found: C, 56.33; H, 3.35; N, 5.02; MW 275.

3-Acetyldithieno[3,4-*b*:3',2'-*d*]pyridine (**6**).

The first fractions from the chromatography described above were concentrated and the residue sublimed at 139°/0.3 mm Hg, giving 37.3 mg (16%) when ether was used as solvent and 28.0 mg (6%) when tetrahydrofuran was used as solvent; mp 177.5-179.0°; ir (potassium bromide): ν CO 1635 cm^{-1}; ^{1}H nmr: δ 9.15 (s, 1H, 5-H), 8.25 (s, 1H, 1-H), 7.87 (d, 1H, 8-H, J = 5.37 Hz), 7.77 (d, 1H, 7-H, J = 5.37 Hz).

Anal. Calcd. for $C_{11}H_7NOS_2$: C, 56.62; H, 3.02; N, 6.00; MW 233.32. Found: C, 56.26; H, 3.14; N, 5.96; MW 233.

1,3-Diformyldithieno[3,4-*b*:3',2'-*d*]pyridine (**7**).

This compound was prepared by analogy with the preparation of **2** from 349 mg (1.00 mmole) and 0.42 ml (5.00 mmoles) of freshly distilled *N,N*-dimethylformamide. After evaporation the residue was chromatographed using ethyl acetate/petroleum ether (1:3) and (1:1) as eluents. 74 mg (30%) was obtained as yellow crystals, after sublimation at 188°/0.40 mm Hg followed by hplc chloroform/methanol (99:1) as eluent. When **7** was prepared according to the procedure used for the preparation of **3** the yield was after hplc using heptane/ethyl acetate/2-propanol (59:40:1) as eluent 232 mg (47%); ir (potassium bromide): ν CO 1640 cm^{-1}; ^{1}H nmr: δ 10.98 (s, 1H, 3-CHO), 10.43 (s, 1H, 1-CHO), 9.27 (d, 1H, 5-H, J = 0.78 Hz), 8.61 (dd, 1H, 8-H, J = 5.33, 0.78 Hz), 8.00 (d, 1H, 7-H, J = 5.33 Hz).

Calcd. for $C_{11}H_5NO_2S_2$: 246.9762; hrms Found: 246.9759.

3-Formyldithieno[3,4-*b*:3',2'-*d*]pyridine (**8**).

This compound, 13 mg (3%), was obtained when tetrahydrofuran was used as solvent. Physical data were identical with those of an authentic sample [5].

3,7-Diformyldithieno[3,4-*b*:3',2'-*d*]pyridine (**9**).

This compound was obtained in a yield of 26.4 mg (12%) when ether was used as solvent and 24.0 mg (5.0%) when

tetrahydrofuran was used as solvent. The physical data of **8** were identical with those of an authentic sample [5].

1,3-(Di-*N,N*-dimethyldithiocarbamoyl)dithieno[3'4-*b*:3',2'-*d*]-pyridine (**10**).

This compound was prepared as described for **2** from 349 mg (1.00 mmole) of **1** and 960 mg (4.00 mmoles) of *N,N,N',N'*-tetramethylthiouram disulfide. Upon work up the reaction mixture was treated with a solution of ammonium chloride/dichloromethane (1:1). The phases were separated and the aqueous phase extracted with dichloromethane. After evaporation the residue was chromatographed using ethyl acetate/petroleum ether (1:3) and (2:1) as eluent giving 143.6 mg of a mixture of **10** and **11**. The mixture could be separated by hplc using heptane/ethyl acetate/2-propanol (65:25:10) as eluent giving 15.5 mg (4%) of **10** as yellow crystals, mp 217.0-219.0°. When tetrahydrofuran was used as solvent the yield of **10** was 240.3 mg (28%); ir (potassium bromide): ν 3400, 1500, 1240, 1150 cm^{-1}; ^1H nmr: δ 9.13 (d, 1H, 5H, J = 0.81 Hz), 8.27 (dd, 1H, 8-H, J = 5.27, 0.81 Hz), 7.79 (d, 1H, H-7, J = 5.27 Hz), 3.64 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.54 (s, 3H, CH_3).

Calcd. for $C_{15}H_{15}N_3S_6$: 428.9590; hrms Found: 428.9591.

3-*N,N*-(Dimethyldithiocarbamoyl)dithieno[3,4-*b*:3',2'-*d*]pyridine (**11**).

The first fractions of the separation described above were concentrated giving 78.1 mg (25%) of **11** as yellow crystals, mp 184.0-186.0°. When tetrahydrofuran was used as solvent only traces were isolated; ^1H nmr: δ 9.11 (d, 1H, 5-H, J = 0.81 Hz), 8.26 (s, 1H, 1-H), 7.83 (dd, 1H, 8-H, J = 5.26, 0.81 Hz), 7.78 (d, 1H, 7-H, J = 5.26 Hz), 3.64 (s, 3H, CH_3), 3.54 (s, 3H, CH_3).

Calcd. for $C_{12}H_{10}N_2S_4$: 309.9727; hrms Found: 309.9728.

Di-1,7-(*N,N*-dimethyldithiocarbamoyl)dithieno[3,4-*b*:3',2'-*d*]-pyridine (**12**).

When tetrahydrofuran was used as solvent for the preparation of **10** the hplc separation using heptane/ethyl acetate/2-propanol (65:25:10) as eluent gave 48.9 mg (6%) of a third component, **12**. This was isolated as yellow crystals mp 199.0-201.0°; ir (potassium bromide): ν 3400, 1500, 1240, 1150 cm^{-1}; ^1H nmr: δ 9.06 (d, 1H, 5-H, J = 0.79 Hz), 8.22 (s, 1H, 1-H), 7.88 (d, 1H, 8-H, J = 0.79 Hz), 3.63 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.54 (s, 3H, CH_3).

Calcd. for $C_{15}H_{15}N_3S_6$: 428.9590; hrms Found: 428.9598.

Di-1,3-(carbomethoxy)dithieno[3,4-*b*:3',2'-*d*]pyridine (**13**).

This compound was prepared by analogy with the preparation for **3** from 698 mg (2.00 mmoles) of **1** in 40 ml of anhydrous tetrahydrofuran and 1.10 ml (12.0 mmoles) of freshly distilled dimethyl carbonate. On workup, the reaction mixture was treated with ice and 1*N* hydrochloric acid/dichloromethane (1:1). After stirring for half an hour the phases were separated, and the aqueous phase was neutralized with a saturated solution of sodium hydrogen carbonate and extracted with dichloromethane. The residue obtained upon evaporation was chromatographed using ethyl acetate/petroleum ether (1:3) and (1:1) as eluents. The main fractions contained **13** and **14**, which were separated by hplc using ethyl acetate/heptane/2-propanol (68:30:2) as eluent, and 221.1 mg (36%) of **13** was obtained. After sublimation at 158°/0.40 mm Hg mp was 192.0-194.0°; ir (potassium bromide): ν CO 1710, 1735 cm^{-1}; ^1H nmr: δ 9.29 (d, 1H, 5-H, J = 0.81 Hz), 8.99 (dd, 1H, 8-H, J = 5.36, 0.81 Hz), 7.88 (d, 1H, 7-H, J = 5.36 Hz), 4.07 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3).

Anal. Calcd. for $C_{13}H_9NO_4S_2$: C, 50.80; H, 2.95; N, 4.56; MW 307.35. Found: C, 50.92; H, 3.03; N, 4.89; MW 307.

Di-3,7-carbomethoxydithieno[3,4-*b*:3',2'-*d*]pyridine (**14**).

In the hplc separation described above, 24.5 mg (4%) of **14** was isolated as yellow crystals, mp 204.0-206.0° after sublimation at 175°/0.8 mm Hg; ir (potassium bromide): ν CO 1710, 1720 cm^{-1}; ^1H nmr: δ 9.26 (d, 1H, 5-H, J = 0.74 Hz), 8.42 (d, 1H, 8-H, J = 0.74 Hz), 8.18 (s, 1H, 1-H), 4.05 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3).

Calcd. for $C_{13}H_9NO_4S_2$: 306.9973; hrms Found: 306.9974.

Reaction of 1,3-Dilithiodithieno[3,4-*b*:3',2'-*d*]pyridine with one Equivalent of Dimethyl Disulfide.

A 250 ml three-necked flask was flushed with nitrogen and charged with 698 mg (2.00 mmoles) of sublimed **1** in 100 ml of anhydrous ether. At -70°, 2.20 ml (4.40 mmoles) of 2*N* butyllithium in cyclohexane diluted with 10 ml of anhydrous ether was added dropwise with stirring. The stirring was continued at -70° for two hours and after one hour at -30° the reaction mixture had a constant composition according to tlc. At 0° the reaction mixture was treated with ice and 1*N* hydrochloric acid. The stirring was continued for half an hour, after which the phases were separated, and the water phase neutralized with a saturated solution of sodium hydrogen carbonate and extracted three times with ether. The combined ether phases were washed with water and dried over magnesium sulfate. After evaporation the residue was chromatographed using ethyl acetate/petroleum ether (1:10) and (1:2) as eluents. The first fractions contained 135.8 mg (24%) of **2**, the middle fractions **15** and **16**, which were separated by hplc using heptane/ethyl acetate/2-propanol (87.5:10:2.5) as eluent, and the last fractions 46 mg (12%) of dehalogenated **2**, giving mp and ir spectrum identical with those of the parent tricycle **17** [8].

3-Thiomethyldithieno[3,4-*b*:3',2'-*d*]pyridine (**15**).

After hplc, 90.2 mg (19%) of **15** was obtained as yellow crystals, which were sublimed at 42°/0.3 mm Hg had a mp 63.0-65.0° (heptane); ^1H nmr: δ 9.03 (d, 1H, 5-H, J = 0.78 Hz), 7.84 (s, 1H, 1H), 7.77 (d, 1H, 7-H, J = 5.20 hz), 7.72 (dd, 1H, 8-H, J = 5.20, 0.78 Hz).

Anal. Calcd. for $C_{10}H_7NS_3$: C, 50.59; H, 2.97; N, 5.90; MW 237.38. Found: C, 50.46; H, 3.04; N, 5.89; MW 237.

1-Thiomethyldithieno[3,4-*b*:3',2'-*d*]pyridine (**16**).

After hplc, 65.5 mg (14%) of **16** was obtained as bright yellow crystals, which were sublimed at 52°/0.3 mm Hg and had a mp 72.0-74.0°; ^1H nmr: δ 8.96 (d, 1H, 5-H, J = 0.71 Hz), 8.59 (dd, 1H, 8-H, J = 5.25, 0.71 Hz), 8.03 (s, 1H, 3-H), 7.83 (d, 1H, 7-H, J = 5.25 Hz).

Anal. Calcd. for $C_{10}H_7NS_3$: C, 50.59; H, 2.97; N, 5.90; MW 237.38. Found: C, 50.71; H, 3.06; N, 5.97; MW 237.

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