Bull. Chem. Soc. Jpn., *57*, *1276—1278 (1984)* [Vol. 57, No. 5

The Willgerodt-Kindler Reaction between Polycyclic Aromatic Amines and Benzaldehyde. Formation of 1,3-Thiazines

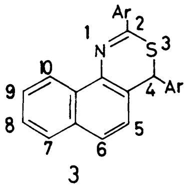
Yujiro Nomura, Takashi Hayama, Yoshito Takeuchi,*
Shuji Tomoda, and Yuko Kato
Department of Chemistry, College of Arts and Sciences, The University of Tokyo,
Komaba, Meguro-ku, Tokyo 153
(Received December 15, 1983)

The title reaction performed under typical conditions of the Willgerodt-Kindler reaction afforded "abnormal" product 1,3-thiazines. A mechanism involving the Diels-Alder reaction between *N*-benzylidenearylamine and thiobenzaldehyde has been suggested to explain the formation of 1,3-thiazines.

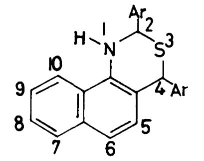
The Willgerodt-Kindler reaction,[1] in which ketones or aldehydes are allowed to react with amines in the presence of elemental sulfur under thermal conditions, is well known as an effective method for the preparation of thioamides. We now report the formation of abnormal products, 1,3-thiazines in the reaction between benzaldehyde and polycyclic aromatic amines under the typical Willgerodt-Kindler conditions[2] and present evidence for the possible intervention of thiobenzaldehyde, an elusive species which has attracted considerable attention in recent years.[3]

Results and Discussion

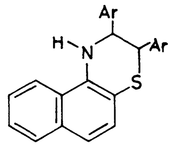
Typical reaction conditions are illustrated by the reaction between 1-naphthylamine (**1**) and benzaldehyde (**2a**). A mixture of **1**, **2a** and an excess powdered sulfur was heated at 140—150 °C for 48 h under a nitrogen atmosphere. Brisk evolution of hydrogen sulfide was evident by the positive test on lead tetraacetate paper during the reaction. The dark viscous reaction mixture was purified by column chromatography to give 2,4-diphenyl-4*H*-naphtho[1,2-*d*][1,3]thiazine (**3a**, 29% yield) and *N*-(1-naphthyl)thiobenzamide (48% yield)[2] in addition to two minor products, 2,4-diphenyl-1,4-dihydro-2*H*-naphtho[1,2-*d*][1,3]thiazine (**4a**, 6% yield) and an unidentifiable compound (11% yield).



3



4



4′

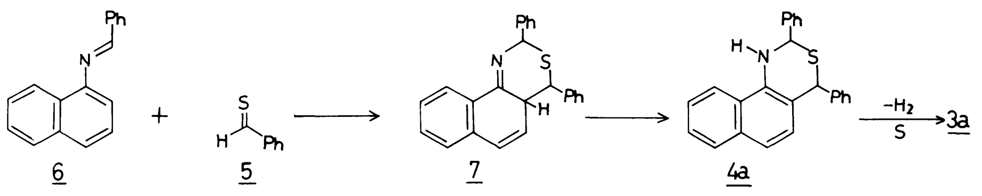
The structures of the 1,3-thiazine (**3a**) and dihydrothiazine (**4a**) were assigned by spectral data (IR, ^{1}H and ^{13}C NMR, MS) and elemental analysis. With regard to the structure of dihydrothiazine (**4a**), the position of the heteroatoms in the thiazine ring system was determined by its ^{1}H NMR data. The proton of C-2 showed up as a doublet (δ 5.26, J=5.5 Hz), whereas that of C-4 appeared as a singlet (δ 5.41). This indicated that the structure of **4a** is more consistent with the 1,3-thiazine ring system represented by formula **4** (Ar=Ph) than structure **4′**. The most explicit evidence for the structure of thiazine (**3a**) was obtained by dehydrogenation of dihydrothiazine (**4a**) over elemental sulfur in refluxing pyridine: **4a** was converted into **3a** in 80% yield.

The reactions between **1** and *p*-substituted benzaldehydes (**2**) are summarized in Table 1. The yield of **3** varies from 24 to 35%. The structures of these compounds **3** were assigned on the basis of spectral (^{1}H and ^{13}C NMR, IR, MS) and analytical data. Although these reactions afforded thioamides as the major product, the formation of **3** is significant since such an easy preparation of 1,3-thiazines has not been reported to date.[4]

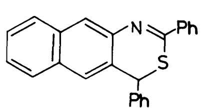
Table 1. Synthesis of 1,3-thiazines (**3**, **12**, **13**, and **14**) from aromatic amines (**1**, **9**, **10**, and **11**)

Amine	ArCHO(**2**)[a]	Reagent/mmol			Conditions	1,3-Thiazine	Yield/%[b]
		1	**2**	S	Temp/°C, Time/h		
1	**2a**	10	20	30	150, 48	**3a**	29
1	**2b**	10	20	22	145, 42	**3b**	35
1	**2c**	10	20	23	145, 41	**3c**	24
9	**2a**	20	40	40	140, 7	**12**	13
10	**2a**	2.6	5.3	5.3	145, 22[c]	**13**	32
11	**2a**	2.8	6.8	6.3	145, 24[c]	**14**	22

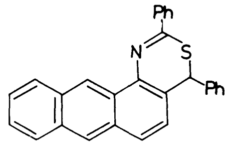
a) **2a**: Benzaldehyde, **2b**: *p*-chlorobenzaldehyde, **2c**: *p*-bromobenzaldehyde. b) Isolated, unoptimized yield. c) In 4-Methylpyridine.



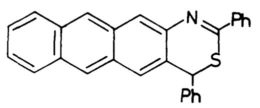
(Eq. 1)



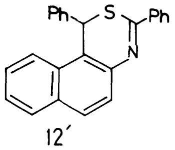
12



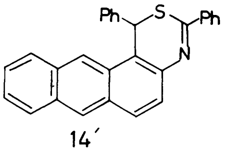
13



14



12′



14′

With a view to extend this reaction to other amines, we were particularly intrigued by the mechanism which might involve thiobenzaldehyde (**5**): It was anticipated that 1,3-thiazine might have arisen from the Diels-Alder reaction between **5** and *N*-benzylidene-1-naphthylamine **6**, a 2-aza-1,3-butadiene in which the C=C bond is incorporated in the naphthalene ring. It is well established that aldehydes react with hydrogen sulfide in the presence of amine to afford thioaldehydes.[5] As shown in Eq. 1, thermal cycloaddition between **5** and **6** would give rise initially to **7**, which undergoes 1,3-H shift to afford dihydrothiazine **4a** (Eq. 1).

Conversion of **4** into **3** under the reaction conditions may be readily understood since **4** was transformed to **3** upon dehydrogenation with elemental sulfur as described earlier. In order to demonstrate possible intervention of **5**, **6** was allowed to react with **5** generated *in situ* from *S*-benzyl phenylmethanethiosulfinate (**8**).[3a] Indeed, when a mixture of **6** and a large excess **8** in toluene was heated at 100 °C for 20 h in the presence of 4A Molecular Sieves, **4a** was isolated in 47% yield. Mixed melting point as well as spectral data (^{1}H NMR and IR) unequivocally established the structure of this product. The formation of the thioamide was not observed in this reaction. It should be noted here that the reaction of 2-aza-1,3-butadiene and thiocarbonyl compound has not previously been reported.[6]

Synthesis of 1,3-thiazines under Willgerodt-Kindler conditions can also be applied to other aromatic amines, such as 2-naphthylamine (**9**), 1-anthrylamine (**10**) and 2-anthrylamine (**11**) (Table 1). Structure assignments of the products (**12**, **13**, and **14**) were based on spectral data (NMR, IR and MS) and combustion analysis. In the cases of **9** and **11**, the structures of the 1,3-thiazines (**12** and **14**, respectively) were more consistent with formulas **12** and **14** rather than with **12′** and **14′**. The absence of IR band near 810 cm^{-1} precluded the possibility of 1,2,3,4-tetrasubstituted benzene ring structures.

In summary, while the yield of 1,3-thiazines is not high, the present reaction as well as the reaction between 2-aza-1,3-diene and thiocarbonyl compound may suggest a useful general entry to 1,3-thiazine system, to which access has been difficult,[4] by appropriate choice of reaction conditions.

Experimental

All reactions were performed under dry nitrogen. Mass spectra were measured with a Hitachi RMU-6MG Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian EM-390 spectrometer and a JEOL FX-90Q spectrometer, respectively, using CDCl$_3$ as solvent. Chemical shifts were recorded in δ scale relative to internal tetramethylsilane. IR spectra were recorded on a JASCO A-102 Spectrometer and the frequencies are given in reciprocal centimeter.

General Procedure of the Willgerodt-Kindler Reactions. The ratio of the reagents and reaction conditions are included in Table 1. Solvent was not used except for the preparation of **13** and **14**, for which 4-methylpyridine was used as the solvent. To a mixture of arylamine and benzaldehyde was added powdered sulfur and the mixture was stirred at 140—150 °C for 7—48 h in an oil bath under a nitrogen atmosphere. The resulting dark brown mixture was dissolved in dichloromethane and the unchanged sulfur was removed by filtration. The filtrate was concentrated and chromatographed on a silica-gel column (dichloromethane: hexane= 1—2:5) to give 1,3-thiazine in the yield shown in Table 1. In the case of **2a**, dihydro-1,3-thiazine **4a** was also separated.

Spectral and analytical data of 1,3-thiazine and **4a** now follow;

3a: Mp 175—176 °C; MS (70 eV) *m/z* 351 (M^+); ^{1}H NMR ($CDCl_3$) δ=5.40 (s, 1H, H-4), 7.15 (s, 5H, Ph), 7.4—7.9 (m, 10H, Ar), and 8.93—9.06 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ=158.4 (s), 141.8 (s), 139.5 (s), 138.5 (s), 133.8 (s), 131.5 (d), 130.5 (s), 128.7 (d), 128.5 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.4 (d), 126.5 (d), 125.6 (d), 124.1 (d), 117.3 (s), and 45.8 (d); IR (KBr) 1540, 1490, 1450, 1235, 940, and 810 cm^{-1}.

Found: C, 82.12; H, 4.89; N, 3.90; S, 9.06%. Calcd for $C_{24}H_{17}NS$: C, 82.02; H, 4.88; N, 3.99; S, 9.12%.

4a: Mp 182—183 °C; MS (70 eV) *m/z* 353 (M^+); ^{1}H NMR ($CDCl_3$) δ=4.80 (br s, 1H), 5.26 (d, *J*=5.5 Hz, 1H), 5.41 (s, 1H), and 7.20—7.96 (m, 16H); ^{13}C NMR ($CDCl_3$) δ=145.2 (s), 139.7 (s), 138.9 (s), 133.8 (s), 129.6 (d), 129.2 (d), 128.9 (d), 128.8 (d), 128.5 (d), 127.7 (d), 127.2 (s), 126.6 (d), 126.3 (d), 125.8 (d), 125.3 (d), 120.3 (d), 118.8 (d), 115.5 (s), 57.5 (d), and 48.2 (d); IR (KBr) 3400, 1565, 1510, 1460, 1400, 1110, and 800 cm^{-1}.

Found: C, 81.54; H, 5.22; N, 3.77;, S, 8.69%. Calcd for $C_{24}H_{19}NS$: C, 81.55; H, 5.42; N, 3.96; S, 9.07%.

3b: Mp 161—162 °C; MS (70 eV) *m/z* 420 (M^+); ^{1}H NMR ($CDCl_3$) δ=5.41 (s, 1H), 6.9—8.1 (m, 13H), and 8.97—9.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=156.6 (s), 140.1 (s), 139.3 (s), 137.7 (s), 136.6 (s), 133.8 (s), 130.4 (s), 129.9 (s), 129.5 (d), 128.9 (d), 128.7 (d), 128.2 (d), 127.6 (d), 126.7 (d), 125.4 (d), 123.9 (d), 116.6 (s), and 45.0 (d); IR (KBr) 1535, 1483, 1232, 1167, 1089, 1010, and 930 cm^{-1}.

Found: C, 68.57; H, 3.45; N, 3.27; S, 7.95; Cl, 17.14%. Calcd for $C_{24}H_{15}NSCl_2$:C, 68.58; H, 3.60; N, 3.33; S, 7.63; Cl, 16.87%.

3c: Mp 140—141 °C; MS (70 eV) *m/z* 509 (M^+); ^{1}H NMR ($CDCl_3$) δ=5.35 (s, 1H), 6.85—8.10 (m, 13H), and 8.76—8.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=140.6 (s), 137.1 (s), 133.8 (s), 131.7 (d), 130.2 (s), 129.6 (d), 129.0 (d), 128.2 (d), 127.6 (d), 126.7 (d), 126.3 (s), 125.3 (d), 124.6 (s), 123.9 (d), 121.8 (s), 116.6 (s), and 45.1 (d); IR (KBr) 1575, 1540, 1483, 1391, 1235, 1070, 1007, and 930 cm^{-1}.

Found: C, 56.64; H, 2.85; N, 2.66; S, 6.40; Br, 31.71%. Calcd for $C_{24}H_{15}NSBr_2$: C, 56.60; H, 2.97; N, 2.75; S, 6.30; Br, 31.38%.

12: Mp 201—202 °C; MS (70 eV) *m/z* 351 (M^+); ^{1}H NMR ($CDCl_3$) δ=6.10 (s, 1H), 7.00 (br s, 5H), 7.47 (m, 5H), 7.92 (m, 4H), and 8.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=158.7, 141.9, 130.0, 133.6, 131.5, 130.3, 129.3, 129.1, 129.0, 128.8, 128.4, 128.4, 127.6, 127.1, 127.0, 126.9, 125.6, 123.2, 115.3, and 41.1; IR (KBr) 1540, 1490, 1445, 1260, 1240, 1195, 975, and 915 cm^{-1}.

Found: C, 82.15; H, 4.67; N, 3.98; S, 9.12%. Calcd for $C_{24}H_{17}NS$: C, 82.02; H, 4.88; N, 3.99; S, 9.12%.

13: Mp 185—186 °C; ^{1}H NMR ($CDCl_3$) δ=5.46 (s, 1H), 7.2 (br s, 6H), 7.41—7.62 (m, 5H), 7.85—8.43 (m, 6H), and 9.54 (s, 1H); IR (KBr) 1541, 1490, 1445, 1230, 1173, 1133, 939, and 795 cm^{-1}.

Found: C, 83.76; H, 4.50; N, 3.75; S, 8.21%. Calcd for $C_{28}H_{19}NS$: C, 83.76; H, 4.77; N, 3.49; S, 7.98%.

14: Mp 250—251 °C; ^{1}H NMR ($CDCl_3$) δ=6.26 (s, 1H), 7.2—8.2 (m, 16H), 8.49 (s, 2H); IR (KBr) 1540, 1492, 1447, 1255, 1170, and 965.

Found: C, 83.55; H, 4.48; N, 3.49; S, 8.23%. Calcd for $C_{28}H_{19}NS$: C, 83.76; H, 4.77; N, 3.49; S, 7.98%.

*Reaction of **4a** with Sulfur to Give **3a**.* To a solution of **4a** (35 mg, 0.1 mmol) in dry pyridine (10 mL) was added excess powdered sulfur and the mixture refluxed for 20 h. The resulting dark resinous material was dissolved in dichloromethane (60 mL). The solution was washed with water, 1 M hydrochloric acid (60 mL), aqueous sodium hydrogencarbonate, and water, dried over magnesium sulfate, and concentrated. The residue was chromatographed on a silica-gel column to give **3a** (28 mg, 80% yield), which was identified by comparison of spectral (IR and ^{1}H NMR) data of authentic **3a**.

*Synthesis of **4a** from **6** and **5** Generated from **8**.* A mixture of **6** (0.39 g, 1.7 mmol) and **8** (4.37 g, 17 mmol)[3a] in toluene (5 ml) was placed in a tube and 4A Molecular Sieves (4 g) was added. The tube was thoroughly purged with dry nitrogen and heated at 100 °C for 20 h. The reaction mixture was filtered to remove the molecular sieves and the filtrate concentrated in vacuo. It was then subjected to column chromatographic separation on silica gel (80 g) eluting with hexane:dichloromethane (10:3) to afford **4a** (280 mg, 47% yield). Mixed melting point, IR and ^{1}H NMR spectral comparison unambiguously established its structure.

References

1) E. V. Brown, *Synthesis,* **1975**, 358.

2) K. Kindler, *Justus Liebigs Ann. Chem.*, **431**, 187 (1923).

3) a) J. E. Baldwin and R. C. G. Ropetz, *Tetrahedron,* **39**, 1487 (1983); b) R. Okazaki, A. Ishii, N. Fukuda, H. Oyama, and. N. Inamoto, *J. Chem. Soc., Chem. Commun.*, **1982**, 1187; c) E. Vedejs and D. A. Perry, *J. Am. Chem. Soc.*, **105**, 1683 (1983); d) E. Vedejs, T. H. Eberlein, and D. L. Varie, *ibid,* **104**, 1445 (1982).

4) Review of 1,3-thiazines; G. Prota, "Organic Compounds of Sulfur, Selenium and Tellurium," The Chemical Society, London (1975).

5) R. Mayer, G. Hiller, M. Nitzschke, and J. Jentzsch, *Angew. Chem., Int. Ed. Engl.*, **2**, 370 (1963).

6) The Diels-Alder reaction of thiocarbonyl compounds itself has been reported previously.[3a,c,d]