Decomposition Reaction of 3-Aryl-6-disubstituted Amino-1,4,2,5-dithiadiazines in the Solid State

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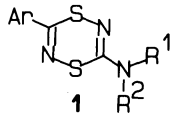
Synopsis. 3-Diethylamino-6-phenyl-1,4,2,5-dithiadiazine, on standing in air at room temperature, decomposed to afford 5-diethylamino-3-phenyl- and 3,5-bis(diethylamino)-1,2,4-thiadiazoles, whereas in the melt and in solution it was remarkably stable. With increasing bulkiness of substituents (Ar and/or NR_2) in 1,4,2,5-dithiadiazines, their stability in the solid state clearly enhanced. Some interstack interactions in the crystal seem to favor the decomposition.

The chemistry of 1,4-dithiins[1] and their aza analogues, 1,4,2-dithiazines,[2] interesting 8π-electron ring systems, has been extensively studied. Higher aza-analogous ring systems, 1,4,2,5-[3] and 1,4,2,6-dithiadiazine isomers,[4] were prepared as diaryl derivatives for the first time in 1984 by two independent groups. Thermal and photochemical decompositions of 3,5-diphenyl-1,4,2,6-dithiadiazine were reported.[4] We have recently prepared unsymmetrically substituted 1,4,2,5-dithiadiazines through a ring expansion of the corresponding 1,4,2-dithiazolium salts by incorporating one nitrogen atom using *N*-unsubstituted sulfenamides[5] or an I_2–NH_3 system.[6] We now report on the stability and decomposition of 3-aryl-6-(disubstituted amino)-1,4,2,5-dithiadiazines (**1**) in the solid state.



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Results and Discussion

Some of 3-aryl-6-(disubstituted amino)-1,4,2,5-dithiadiazines, when allowed to stand in air at room temperature, gradually decomposed to give a colorless oil, in contrast to the high stability of 3,6-diaryl-1,4,2,5-dithiadiazines under similar conditions.[3] The decomposition was monitored by following the color fading of yellow crystal and by TLC. Decomposition times, as required for crystalline compounds to be completely decomposed, are listed in Table 1. In the melt and in solution, on the contrary, dithiadiazines **1** were all remarkably stable. For example, compound **1c** was completely recovered after a week in the melt at 76 °C (>mp 71.5 °C) and after a few months in CH_2Cl_2, MeCN, or EtOH. Thus the stability of **1** depends markedly on the phases.

1,4,2,5-Dithiadiazines, which, if planar, would show the 8π-antiaromatic character, actually assume a boat-like conformation[3b,5] common to 1,4-dithiins,[1] which accounts for the thermal stability of the electron rich π-system. The authors speculate that the boat-shaped structure (characterized especially by the fold angle of hetero-ring and the bulkiness of substituents) will have an effect on the mode of stacking with varying intermolecular interactions which either favors or disfavors the observed decomposition, and that the close intermolecular contact in crystal will result in an increase in the fold angle to instabilize the dithiadiazine ring system itself.

Based on the above speculation, the stability of **1** is expected to be dependent on the electron-donating nature of disubstituted amino groups, which seems to be related to the fold angle. The stability of **1a—f** bearing different disubstituted amino groups and the same phenyl group at the C-3 and C-6 positions, respectively, was examined (Entries 1—6). The electron-donating ability of disubstituted amino groups can be estimated from the basicity of the corresponding secondary amines, and accordingly the data are arranged in the decreasing order of pK_a values.[7] However, there is no correlation between the stability of **1** and the electron-donating ability of substituents.

In order to obtain additional information concerning the electron density on the ring carbons C-3 and C-6, ^{13}C NMR spectra were measured. The chemical shifts for ring carbon bearing Ph and that bearing NR_2 are clearly dependent on the nature of disubstituted amino groups, but bear no correlation to the stability of **1**.

We turn our attention to the steric effect of substituents. It can be seen from Entries 1—6 that **1b**, **e**, and **f** bearing rather bulky substituents, diisopropylamino, morpholino, and *N*-methylphenylamino groups, respectively, are stable, whereas **1c** and **1d** bearing the smaller diethylamino and dimethylamino groups, respectively, have lower stability. The introduction of methoxyl or chloro group on the para-position of the phenyl group in **1a** enhanced the stability of crystal (Entries 7 and 8). Furthermore, the substitution of bulky aryl groups for the phenyl group in **1c**, with the small diethylamino group at the other position kept intact, also tends to retard the decomposition (Entries 10—14).

From the above results, the difference in stability among **1** in the solid state proved to be ascribable to the steric effect of substituents at the C-3 and C-6 positions rather than to their electronic effect.

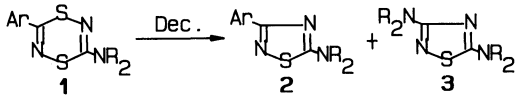
In order to obtain further information on the decomposition, we examined products attributable to decomposition fragments; the results are presented in Table 2. Compound **1c** decomposed in the solid state to afford 5-diethylamino-3-phenyl-1,2,4-thiadiazole (**2a**) and 3,5-bis(diethylamino)-1,2,4-thiadiazole (**3a**), together with considerable amounts of benzonitrile and elemental sulfur. The formation of **2a** is rationalized by thermal elimination of sulfur (position 1 in **1c**) from the unstable 8π-electron ring system to

Table 1. Stability of 1,4,2,5-Dithiadiazines **1** in the Solid State

Entry	1,4,2,5-Dithiadiazines **1**				Dec. time[b]	^{13}C NMR[c]	
	No.	Ar	NR^1R^2	(pK_a)[a]	d	Ar-C	R^1R^2N-C
1	**1a**	Ph		(11.12)	10		
2	**1b**	Ph	N^iPr_2	(11.05)	Stable	177.5	161.6
3	**1c**	Ph	NEt_2	(10.94)	0.5	177.0	162.5
4	**1d**	Ph	NMe_2	(10.73)	0.5	176.0	163.6
5	**1e**	Ph		(8.33)	Stable	176.0	163.2
6	**1f**	Ph	NMePh	(4.85)	Stable	173.4	161.1
7	**1g**				Stable[d]		
8	**1h**				Stable[d]	175.5	163.5
9	**1i**				Stable	175.0	163.4
10	**1j**		NEt_2		6		
11	**1k**		NEt_2		0.5	176.7	162.6
12	**1l**		NEt_2		0.5		
13	**1m**	 [e]	NEt_2		3		
14	**1n**		NEt_2		3		

a) The pK_a value of secondary amine HNR^1R^2 in aqueous solution at 25 °C. b) The time in which crystals have been completely decomposed. c) The assignment of the two quaternary carbons was based on results of 2D COLOC.[13] d) Decomposition was observed after several months. e) Phenylene form.

Table 2. Decomposition Reaction of 1,4,2,5-Dithiadiazines **1** in the Solid State and in the Melt

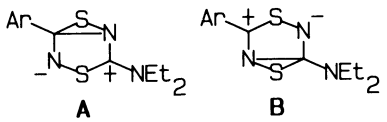


1 **2** **3**

Compd	Conditions	Product yield/%[a]	
		2	**3**[b]
1c	Solid/r.t./0.5 d	15	72
1c	Melt/200 °C/0.5 h	21	28
1c	$+Ph_3P$/r.t./20 d[c]	44	3
1d	Solid/r.t./0.5 d	5	54
1j	Solid/r.t./6 d	18	69
1n	Solid/r.t./3 d	—	92
1f	Melt/200 °C/2 h	25	11

a) ArCN and S_8 were also formed in considerable amounts. b) Conversion yield based on **1**. c) A 1:1 solid mixture of **1c** and Ph_3P.

afford the more stable 6π-electron one. Such a sulfur extrusion is common to 6-membered 8π-electron ring systems such as 1,4-dithiins[1b,c] and 1,4,2-dithiazines.[2] On the other hand, the formation of **3a** is unique and requires a more complex pathway, because two diethylamino groups are introduced on the 1,2,4-thiadiazole ring. Although 3,5-diphenyl-1,2,4-thiadiazole was not formed, one other product was separated by TLC in a trace amount. It seems to be 3-diethylamino-5-phenyl-1,2,4-thiadiazole, an isomer of **2a**, merely because of the presence of the molecular ion peak at *m/z* 233 (100%) in mass spectrum. The selectivity of the sulfur extrusion can be interpreted in terms of considerable contribution of valence isomer **A** leading to **2a**, compared with **B**, owing to the higher electron-donating ability of diethylamino group than that of phenyl group. Other unstable dithiadiazines **1d**, **j**, and **n** also decomposed to afford **3** as a main product.



A **B**

Compound **1c**, which is stable in the melt, decomposed at higher temperature. When heated at 200 °C for 30 min, **1c** was completely decomposed to afford a black oil comprised of **2a** (21%) and **3a** (28%). A 1:1 solid mixture of **1c** and Ph_3P, which was prepared by evaporation of their CH_2Cl_2 solution and allowed to stand in air, slowly decomposed to afford **2a** in 44% yield as a main product and a small amount of **3a**, with triphenylphosphine sulfide formed as expected. It was further found that the stable derivative **1f** also decomposed when heated at 200 °C for 2 h to give the corresponding two 1,2,4-thiadiazole deriva-

tives **2c** and **3c** in low yields.

Information concerning the solid state structure of unstable derivatives has been difficult to obtain. However, an X-ray analysis of stable 3-(*p*-chlorophenyl)-6-morpholino-1,4,2,5-dithiadiazine was successfully performed in our previous work.[5] Direct overlapping occurs between the dithiadiazine rings (head to head with an S···S′ separation of 4.06 Å), but the formation of **3** cannot be directly predicted by the molecular orientation. At present, we believe that this decomposition proceeds much faster in the geometrically fixed crystal in which some interstack interactions favor unimolecular and bimolecular decompositions leading to **2** and **3**, respectively. For detailed interpretation of the mechanism for the formation of **3**, further investigations are needed. This decomposition is also attractive as an alternative synthetic method for 3,5-bis(disubstituted amino)-1,2,4-thiadiazoles, which are limitedly accessible by other methods.[8] Further studies on the decomposition in solution, including photolysis, are in progress.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Hitachi R-40 and a JEOL FX-90A spectrometer, respectively, in $CDCl_3$, using TMS as an internal standard. Two-dimensional $^1J_{CH}$ shift-correlation spectra and long-range ($^nJ_{CH}$) shift-correlation spectra (COLOC) were recorded on a Bruker AC 200P spectrometer at 50.13 MHz for ^{13}C. Mass spectra were taken on a Hewlett Packard 5995A spectrometer by the electron impact ionizing technique at 70 eV.

3-Aryl-6-(disubstituted amino)-1,4,2,5-dithiadiazines **1** were prepared from the corresponding 1,4,2-dithiazolium salts using our reported procedures, and recrystallized from appropriate solvents (MeCN–ether, CH_2Cl_2–hexane, etc.).[5,6]

Decomposition Reaction of 1. Decomposition reactions of **1** (1 mmol) were carried out in the solid state at room temperature or in the melt at 200 °C. Decomposition times are listed in Tables 1 and 2. Crude products were purified by preparative TLC on silica gel. Their yields are presented in Table 2.

5-Diethylamino-3-phenyl-1,2,4-thiadiazole 2a:[9] ^{1}H NMR δ=1.28 (6H, t, J=7.2 Hz), 3.53 (4H, q, J=7.2 Hz), 7.4—7.6 (3H, m), and 8.2—8.3 (2H, m); MS *m/z* (rel intensity) 233 (M^+; 43), 149 (100), 135 ($PhCNS^+$; 72), and 130 (Et_2NCNS^+; 37).

5-Dimethylamino-3-phenyl-1,2,4-thiadiazole 2b:[10] ^{1}H NMR δ=3.19 (6H, s), 7.4—7.6 (3H, m), and 8.2—8.3 (2H, m); MS *m/z* (rel intensity) 205 (M^+; 47), 149 (100), 135 ($PhCNS^+$; 64), and 102 (Me_2NCNS^+; 62).

5-(*N*-Methylphenylamino)-3-phenyl-1,2,4-thiadiazole 2c:[10] ^{1}H NMR δ=3.64 (3H, s), 7.0—7.7 (8H, m), and 8.2—8.3 (2H, m); MS *m/z* (rel intensity) 267 (M^+; 85), 164 ($MePhNCNS^+$; 49), and 135 ($PhCNS^+$; 100).

3-(*p*-*t*-Butylphenyl)-5-diethylamino-1,2,4-thiadiazole 2d: Mp 45.5—47.0 °C; ^{1}H NMR δ=1.28 (6H, t, J=7.2 Hz), 1.34 (9H, s), 3.53 (4H, q, J=7.2 Hz), 7.45 and 8.16 (2H×2, d, J=8.5 Hz); MS *m/z* (rel intensity) 289 (M^+; 86), 274 (94), and 130 (Et_2NCNS^+; 100).

3,5-Bis(diethylamino)-1,2,4-thiadiazole 3a: oil; ^{1}H NMR δ=1.17 and 1.23 (6H×2, t, J=7.2 Hz), 3.41 and 3.53 (4H×2, q, J=7.2 Hz); ^{13}C NMR δ=12.68 (q), 13.60 (q), 43.12 (t), 45.70 (t), 167.72 (s), and 181.67 (s); MS *m/z* (rel intensity) 228 (M^+; 67) and 72 (Et_2N^+; 74).

3,5-Bis(dimethylamino)-1,2,4-thiadiazole 3b:[11] ^{1}H NMR δ=3.06 and 3.08 (6H×2, s); ^{13}C NMR δ=38.65 (q), 39.87 (q), 169.19 (s), and 183.38 (s); MS *m/z* (rel intensity) 172 (M^+; 100), 129 (62), and 102 (Me_2NCNS^+; 98).

3,5-Bis(*N*-methylphenylamino)-1,2,4-thiadiazole 3c:[12] ^{1}H NMR δ=3.50 and 3.54 (3H×2, s), and 7.0—7.6 (10H, m); ^{13}C NMR δ=39.03 (q), 40.47 (q), 124.00 (d), 124.09 (d), 127.01 (d), 128.47 (d), 129.83 (d), 144.92 (s), 146.05 (s), 166.32 (s), and 182.95 (s); MS *m/z* (rel intensity) 296 (M^+; 79), 190 (M^+—MePhN; 59), 164 ($MePhNCNS^+$; 16), 132 ($MePhNCN^+$; 22), and 82 (100).

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References

1) a) K. Kobayashi, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 642 (1982). b) K. Kobayashi, K. Mutai, and H, Kobayashi, *Tetrahedron Lett.*, **1979**, 5003. c) J. Nakayama, M. Kashiwagi, R. Yomoda, and M. Hoshino, *Nippon Kagaku Kaishi*, **1987**, 1424.

2) J. Nakayama, A. Sakai, A. Tokiyama, and M. Hoshino, *Tetrahedron Lett.*, **24**, 3729 (1983); E. Fanghänel, *J. Prakt. Chem.*, **318**, 127 (1976).

3) a) B. G. Lenz and B. Zwanenburg, *J. Chem. Soc., Chem. Commun.*, **1984**, 1386. b) J. M. M. Smits, P. T. Beurskens, B. G. Lenz, and B. Zwanenburg, *Acta Crystallogr., Sect. C*, **41**, 1086 (1985).

4) S. T. A. K. Daley, C. W. Rees, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, **1984**, 57; S. T. A. K. Daley and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 207.

5) K. Yonemoto, I. Shibuya, and K. Honda, *Bull. Chem. Soc. Jpn.*, **61**, 2232 (1988).

6) K. Yonemoto and I. Shibuya, *Chem. Lett.*, **1989**, 89.

7) J. W. Smith, "Basicity and Complex Formation" in "The Chemistry of the Amino Group," John Wiley & Sons, London (1968), Chap. 4, pp. 161—204; "Dissociation Constants of Organic Bases in Aqueous Solution" in "CRC Handbook of Chemistry and Physics," 67th ed, ed by R. C. Weast, CRC Press, Inc., Florida (1986), P. D-159.

8) F. Kurzer, *Adv. Heterocycl. Chem.*, **32**, 285 (1982).

9) H. Grube and H. Suhr, *Chem. Ber.*, **102**, 1570 (1969).

10) J. Goerdeler and K. H. Heller, *Chem. Ber.*, **97**, 225 (1964).

11) J. E. Oliver, *J. Org. Chem.*, **36**, 3465 (1971).

12) A. R. Butler, C. Glidewell, I. Hussain, and P. R. Maw, *J. Chem. Res. (M)*, **1980**, 1843.

13) H. Kessler, C. Griesinger, J. Zarbock, and H. R. Loosli, *J. Magn. Reson.*, **57**, 331 (1984).