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REACTIONS OF 2,4,6-TRIARYL-DIHYDRO-1,3,5-DITHIAZINES WITH ELECTROPHILIC REAGENTS

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2,4,6-Triaryl-dihydro-1,3,5-dithiazines reacted with electrophilic reagents such as p-TsOH·H_2O, CF_3COOH, HCl, and $BF_3.OEt_2$ under reflux in CH_3CN to afford α-2,4,6-triaryl-1,3,5-trithianes and β-isomers (3a-d) in good yields. Reactions with I_2 gave selectively 3a-d in high yields, while with ICl or IBr gave 3a-d and p-substituted benzylideneamine·HY.

Dihydrodithiazines are very useful for the additives[1] of foods, tabacco, soups, etc., and a number of preparations for them have been reported. Reactions for the dihydrodithiazines, however, have scarcely been studied except in a few reports,[2-4] perhaps due to their complicated behavior toward various reagents. We have found that 2,4,6-triaryl-dihydro-1,3,5-dithiazines reacted with amines such as liquid ammonia or methylamine at room temperature to give the corresponding thiobenzamides and dibenzyldisulfides. These products were thought to be formed through unstable thiobenzaldehydes generated by retro[2+2+2] of dihydrodithiazines induced by amines. It was expected that the attack of electrophilic reagents to nitrogen or sulfur atom in the 2,4,6-triaryl-dihydro-1,3,5-dithiazines 1a-d would also form the corresponding thiobenzaldehydes.

It was found that 1a-d reacted with electrophilic reagents such as p-TsOH.H_2O, CF_3COOH, HCl, $BF_3.OEt_2$, I_2, ICl, and IBr in organic solvents at room temperature or reflux to afford the corresponding α-2,4,6-triaryl-1,3,5-trithianes 2a-d and β-isomers 3a-d in good yields. The typical procedure of the reaction of 2,4,6-triphenyl-dihydro-1,3,5-dithiazine 1a with $BF_3.OEt_2$ was described below. A solution of 1a 175 mg (0.5 mmol) and $BF_3.OEt_2$ 142 mg (1 mmol) in CH_3CN (5 ml) was stirred at reflux for 2 h. 10% NaOH solution was added to the reaction mixture, and β-2,4,6-triphenyl-1,3,5-trithiane 3a was obtained in 75% yield. The filtrate was extracted with CH_2Cl_2 (20 ml x 3). After removal of CH_2Cl_2, the residue was separated by silica gel column chromatography using CCl_4 as an eluent to give α-2,4,6-triphenyl-1,3,5-trithiane 2a in 20% yield and benzaldehyde.

The results of the reactions with p-TsOH.H_2O, CF_3COOH, HCl, and $BF_3.OEt_2$ and with I_2, ICl, and IBr are shown in Table 1 and Table 2, respectively. 1a reacted with 36% HCl in CH_3CN at room temperature for 1 h to afford 2,4,6-triphenyl-dihydro-1,3,5-dithiazine·HCl 4a[5] in 91% yield. 4a was allowed to react in CH_3CN at reflux for 5 h giving α-trithiane 2a and β-isomer 3a in 26 and 30% yields respectively. This result showed that trithiane 2a and 3a were formed via thiobenzaldehyde[6] arising from the fragmentation of 4a. Hard electrophilic reagents[7, 8] such as p-TsOH.H_2O, CF_3COOH, HCl, and $BF_3.OEt_2$ initially reacted with nitrogen atom in 1a-d, followed by a scission to form Schiff bases and thiobenzaldehydes.

Table 1. Reactions of 2,4,6-Triaryl-dihydro-1,3,5-dithiazines (1a-d) with Electrophilic reagents[a)]

Run	Substrate	Electrophilic reagent (equiv.)	Solvent	Time/h	Yield/% 2[9)]	Yield/% 3[10)]
1	1a	p-TsOH.H_2O (1)	CH_2Cl_2	10	30	26
2	1b	p-TsOH.H_2O (1)	CH_2Cl_2	10	34	36
3	1c	p-TsOH.H_2O (1)	CH_2Cl_2	10	7	54
4	1d	p-TsOH.H_2O (1)	CH_2Cl_2	10	15	55
5	1a	CF_3COOH (1)	CH_2Cl_2	5	17	16
6	1a	HCl (excess)	CH_3CN	5	25	30
7	1a	$BF_3.OEt_2$ (2)	CH_3CN	2	25	70
8	1b	$BF_3.OEt_2$ (2)	CH_3CN	2	25	60
9	1c	$BF_3.OEt_2$ (2)	CH_3CN	2	18	67
10	1d	$BF_3.OEt_2$ (2)	CH_3CN	2	11	57
11[b)]	1a	$BF_3.OEt_2$ (4)	CH_3CN	5	0	26

a) Substrate : 0.5 mmol, Solvent : 5 ml, Temp : reflux, p-Substituted benzaldehydes were obtained in all runs.

b) In the presence of 2,3-dimethylbutadiene (5 equiv.), the adduct 8 was obtained in 53% yield.

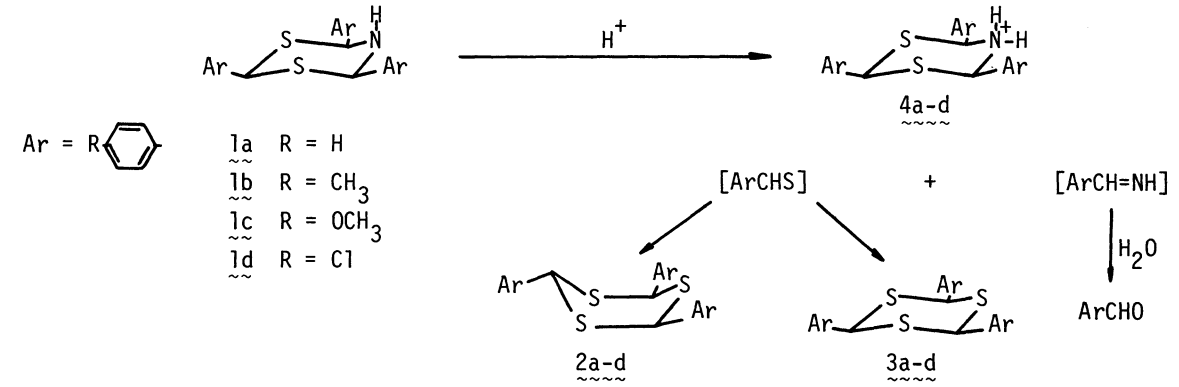
Table 2. Reactions of 2,4,6-Triaryl-dihydro-1,3,5-dithiazines (1a-d) with Halogens[a)]

Run	Substrate	Halogen (equiv.)	Time/h	Yield/% 3
1	1a	I_2 (0.5)	48	58
2	1a	I_2 (1)	48	72
3	1b	I_2 (1)	5	93
4	1c	I_2 (1)	5	84
5	1d	I_2 (1)	5	79
6	1a	ICl (1)	5	32
7	1b	ICl (1)	5	56
8	1c	ICl (1)	5	25
9[b)]	1d	ICl (1)	5	52
10[c)]	1a	IBr (1)	5	75
11[c)]	1a	IBr (2)	5	52
12[c)]	1a	IBr (3)	5	0
13[c)]	1b	IBr (1)	5	24
14	1c	IBr (1)	5	39
15[c)]	1d	IBr (1)	5	39

a) Substrate : 0.5 mmol, CH_2Cl_2 : 5 ml, Temp : room temperature, p-substituted benzaldehydes were obtained in all runs.

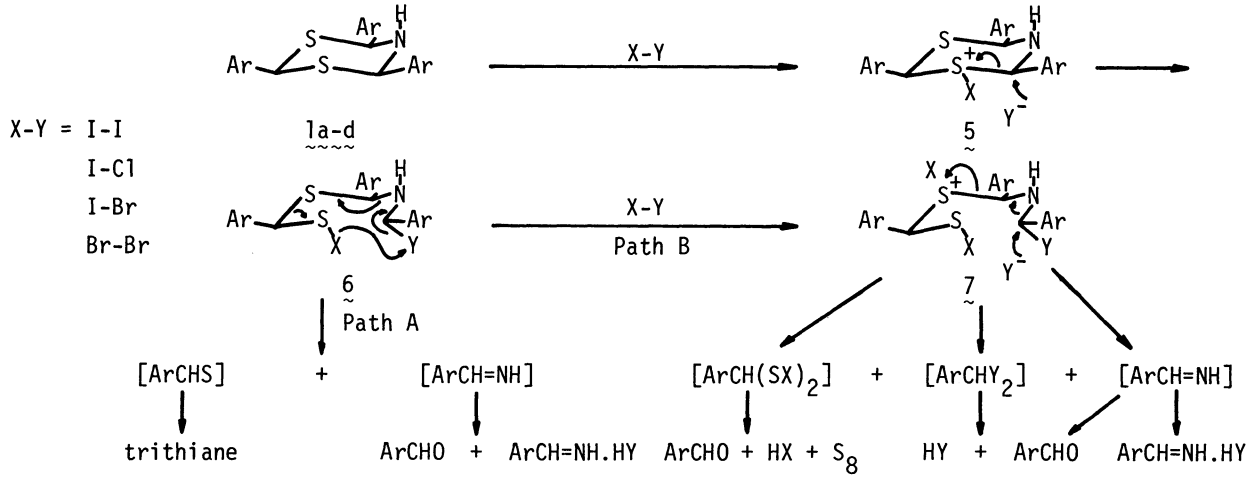
b) Benzylideneamine.HCl was obtained.

c) p-Substituted benzylideneamine.HBr were obtained.



Scheme 1.

1a-d reacted with I_2 to afford β-trithianes 3a-d and benzaldehydes, while the reactions with ICl or IBr gave 3a-d and benzaldehydes besides the corresponding benzylideneamine·HY. In the case of Br_2 in CH_2Cl_2 at 0 °C, the corresponding benzylideneamine·HBr and benzaldehydes were formed and no trithianes were obtained. A possible mechanism of the reactions of 1a-d with halogens and interhalogen compounds is shown in Scheme 2.

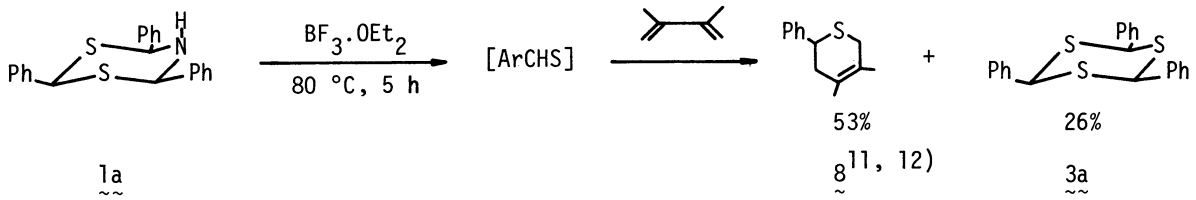


Scheme 2.

When dihydrodithiazine 1b was heated in benzene at reflux for 8 h, it was recovered quantitatively. This shows that 1b is considerably stable to heat. However, the reactions with I_2 proceeded readily at room temperature to give trithianes 3a-d in high yields. Apparently 1a-d are activated by the interaction of I_2 with nitrogen or sulfur atom in 1a-d. Since I_2, Br_2, ICl, and IBr are soft acids,[7, 8] these electrophilic reagents would react with sulfur atom in 1a-d to form sulfonium salt 5. Then the ring opening of 5 takes place by the attack of a counter anion to 4-position to give intermediate 6, and the subsequent scission of 6 generates a thiobenzaldehyde and a Schiff base (Path A in Scheme 2). The thiobenzaldehyde trimerizes to form trithiane.[6] When X and Y consist of a soft base and a soft acid, respectively, as iodine does, Path A occurs preferentially. Over 50% of 3a was obtained by the reaction with I_2 of 0.5 equiv. to 1a (Run 1 in Table 2). This finding is in accord with the fact that the Path A contains a regeneration of I_2. When X and Y are a borderline base and a soft acid, respectively, as bromine is, the reaction via sulfonium salt 7 would occur preferentially and trithianes were not obtained.

An attempt to trap thiobenzaldehyde was successful in the reaction of 1a (1 mmol) with $BF_3.OEt_2$

(4 mmol) in the presence of 2,3-dimethylbutadiene (5 mmol) in CH_3CN (5 ml) at 80 °C (in titanium autoclave) for 5 h, apparently implying that thiobenzaldehydes were initially generated in the series of reactions with electrophilic reagents.



1a 8[11, 12] 3a

Scheme 3.

Work along the expansion of synthetic utilities using dihydrodithiazines are in progress in our laboratory.

References

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5) 2,4,6-Triphenyl-dihydro-1,3,5-dithiazine.HCl 4a ; mp 155-156 °C, NMR(DMSO-d_6) : δ 5.78(s, 2H, CH), 6.01(s, 1H, CH), 6.60(br. s, 2H, $\overset{+}{N}H_2$), 7.30-7.67(m, 15H, Ph), IR(KBr) : 2400 cm^{-1}(ν $\overset{+}{N}H_2$).

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9) 2a (R=H) ; mp 163-4 °C(lit. 167 °C), NMR($CDCl_3$) : δ 5.40(s, 2H, CH), 5.68(s, 1H, CH), 7.18-7.51 (m, 13H, Ph), 7.81-7.92(m, 2H, Ph), MS(m/e) : 366(M^+), 2b (R=CH_3) ; mp 149 °C(lit. 149-150 °C), NMR($CDCl_3$) : δ 2.30(s, 6H, CH_3), 2.37(s, 3H, CH_3), 5.36(s, 2H, CH), 5.62(s, 1H, CH), 7.07(d, 4H, Ar, J=8 Hz), 7.21(d, 2H, Ar, J=8 Hz), 7.27(d, 4H, Ar, J=8 Hz), 7.70(d, 2H, Ar, J=8 Hz), MS(m/e) : 408(M^+), 2c (R=OCH_3) ; mp 127 °C(lit. 127 °C), NMR($CDCl_3$) : δ 3.77(s, 6H, OCH_3), 3.84(s, 3H, OCH_3), 5.36(s, 2H, CH), 5.64(s, 1H, CH), 6.82(d, 4H, Ar, J=8 Hz), 6.92(d, 2H, Ar, J=8 Hz), 7.33 (d, 4H, Ar, J=8 Hz), 7.55(d, 2H, Ar, J=8 Hz), MS(m/e) : 152(1/3M^+), 2d (R=Cl) ; mp 163-164 °C, NMR($CDCl_3$) : δ 5.30(s, 2H, CH), 5.61(s, 1H, CH), 7.28(s, 12H, Ar), MS(m/e) : 153(1/3M^+).

10) 3a (R=H) ; mp 222-223 °C(lit. 225 °C), NMR(DMSO-d_6) : δ 5.80(s, 3H, CH), 7.39(s, 15H, Ph), MS(m/e) : 366(M^+), 3b (R=CH_3) ; mp 179-180 °C(lit. 180 °C), NMR(DMSO-d_6) : δ 2.28(s, 9H, CH_3), 5.67(s, 3H, CH), 7.12(d, 6H, Ar, J=8 Hz), 7.27(d, 6H, Ar, J=8 Hz), MS(m/e) : 408(M^+), 3c (R=OCH_3) ; mp 182-183 °C(lit. 183 °C), NMR(DMSO-d_6) : δ 3.73(s, 9H, OCH_3), 5.64(s, 3H, CH), 6.88(d, 6H, Ar, J=8 Hz), 7.31(d, 6H, Ar, J=8 Hz), MS(m/e) : 152(1/3M^+), 3d (R=Cl) ; mp 173 °C, NMR(DMSO-d_6) : δ 5.82(s, 3H, CH), 7.37(s, 12H, Ar), MS(m/e) : 153(1/3M^+).

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12) 8 ; oily matter, NMR($CDCl_3$) : δ 1.73(br. s, 6H, CH_3), 2.36-2.63(m, 2H, PhCH-CH_2), 2.86(br. d, 1H, SCH_2C=, J=17 Hz), 3.43(br. d, 1H, SCH_2C=, J=17 Hz), 3.94(dd, 1H, PhCHS, J=6, 9 Hz), 7.20-7.35(m, 5H, Ph), MS(m/e) : 204(M^+).

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