RING TRANSFORMATION OF 3,6-DIARYL-1,2,4,5-TETRAZINES TO 3,6-DIARYLPYRIDAZINES AND 2,5-DIARYL-1,3,4-THIADIAZOLES BY ELEMENTAL SULFUR AND AMINES

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Abstract: The reaction of 3,6-diaryl-1,2,4,5-tetrazines with elemental sulfur and amines in refluxing toluene gave 3,6-diaryl-1,4-dihydrotetrazines, 3,6-diarylpyridazines, or 2,5-diaryl-1,3,4-thiadiazoles, depending on the type of substituents of the 1,2,4,5-tetrazines and amines.

Introduction

1,2,4,5-Tetrazines are well known heterodienes involved in the inverse electron demand Diels-Alder reaction (1) and have been widely used for the preparation of heterocycles (2). Moreover, some ring transformations by nucleophiles have been studied because of the electrophilicity of the C-3 and C-6 positions of the ring; the reaction of 1,2,4,5-tetrazines with the enolate anions of acyclic and cyclic carbonyls gave pyridazines (3) and 1,2-diazocines (4). Pyridazines were also obtained by the reaction with the α-carbanions of imines (5). 2-Pyrazolin-5-ones were formed by the initial nucleophilic attack of potassium hydroxide at the C-3 position of 3,6-bis(α-hydroxybenzyl)-1,2,4,5-tetrazines (6). However, treatment of 3,6-dibenzyl-1,2,4,5-tetrazine with potassium hydroxide yielded imidazolo[1,2-*b*]-1,2,4,5-tetrazines (7). The occurence of S_N (ANRORC) mechanism in the hydrazination of 1,2,4,5-tetrazines was reported (8). In our previous papers we reported the ring transformations of 1,2,4,5-tetrazines to pyrazoles or 1,2,4-triazines by silicon reagents such as cyanotrimethylsilane (9), trimethylsilyl isothiocyanate (10), or *N*-(trimethylsilyl)aldimines (11). There has appeared no report on the ring transformation of 1,2,4,5-tetrazines using sulfur reagents. It is known that elemental sulfur reacts with amines to form "activated" sulfur species, which behave as the nucleophilic species "N" or the electrophilic species "E" (12).

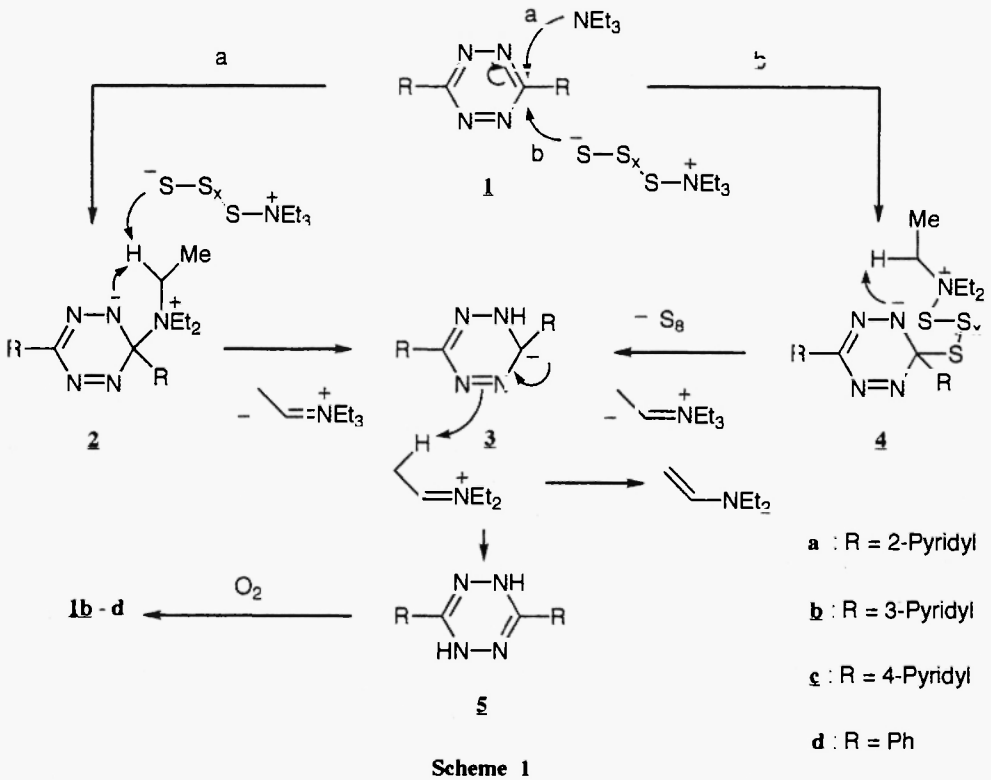
$$S_8 + R_3N \rightleftharpoons \underset{\text{("N")}}{R_3N^+\text{-}S\text{-}S_x\text{-}S^-} \overset{BH}{\rightleftharpoons} R_3N + \underset{\text{("E")}}{^+S\text{-}S_x\text{-}SH}$$

The "activated" sulfur species played an important role in the reactions of unsaturated carbonyl compounds (12) or ω-phenylpropiophenone (13) with sulfur in the presence of amines. We became

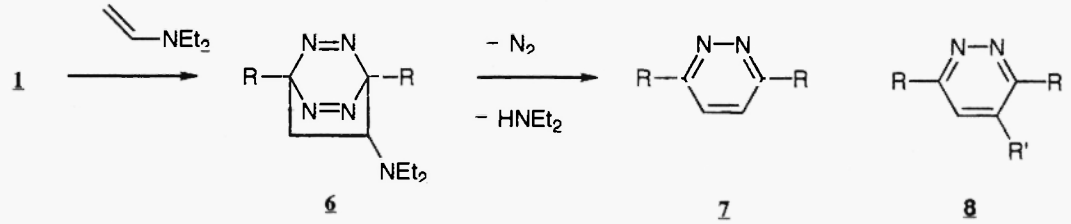
interested in the utilization of this nuceophilic sulfur species for the ring transformation of heterocycles. 1,2,4,5-Tetrazines seem suitable for this purpose because of the versatile reactivities towards electrophiles as previously mentioned. We would now like to report a new ring transformation of 1,2,4,5-tetrazines to pyridazines and 1,3,4-thiadiazoles using elemental sulfur and amines.

Results and Discussion

A mixture of 3,6-diaryl-1,2,4,5-tetrazine **1**, elemental sulfur, and triethylamine in toluene was refluxed. 3,6-Bis(2-pyridyl)-1,2,4,5-tetrazine **1a** gave 3,6-di(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine **5a** and 3,6-bis(2-pyridyl)pyridazine **7a**, while **1b-d** afforded the corresponding 3,6-diarylpyridazines **7b-d** (Schemes 1 and 2). They were also formed without sulfur, but it took more time to finish the reaction



Scheme 1



Scheme 2

Table 1: Reaction conditions (a), products, and yields

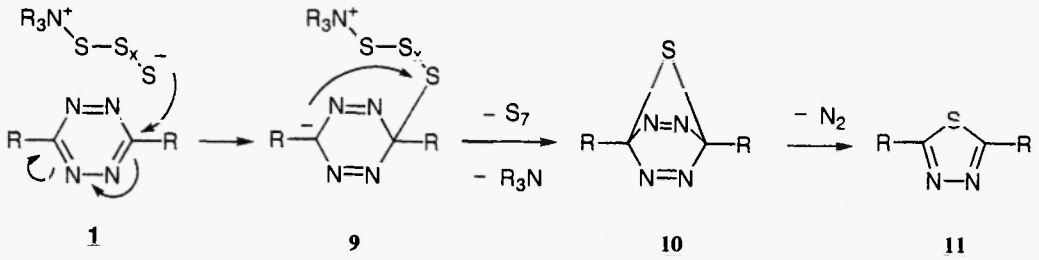
Run	1	Amines	Molar ratio 1 : S_8 : Amine	Reaction time (h)	5 %	7 %	11 %
1 (b)	**a**	Et_3N	1 : 0 : 50	39	21	34	-
2 (b)			1 : 2 : 50	15	28	56	trace
3 (b)		morpholine	1 : 0 : 10	4	inseparable mixture		
4 (b)			1 : 2 : 10	4	3	-	26
5	**b**	Et_3N	1 : 0 : 50	30	-	29	-
6			1 : 2 : 50	16	-	34	-
7		morpholine	1 : 0 : 10	100	recovery of **1b**		
8			1 : 2 : 10	100	recovery of **1b**		
9	**c**	Et_3N	1 : 0 : 50	31	-	39	-
10			1 : 2 : 50	12	-	69	trace
11		morpholine	1 : 0 : 10	90	inseparable mixture		
12 (b)			1 : 2 : 10	90	-	-	17
13 (b)	**d**	Et_3N	1 : 0 : 50	100	-	68	-
14 (b)			1 : 2 : 50	23	-	63	-
15		morpholine	1 : 0 : 10	20	recovery of **1d**		
16			1 : 2 : 10	20	recovery of **1d**		

(a) A mixture of **1** (1.0 mmol) and amine in the presence or absence of sulfur in toluene (40 ml) was refluxed.

(b) The reaction mixture was separated by column chromatography.

and the yields were lower (Table 1). The combinations of sulfur and other alkylamines such as diethylamine, tripropylamine, butylamine, morpholine, piperidine, or pyrrolidine were examined to improve the yield and to obtain 4-alkyl-3,6-diarylpyridazines **8** and sulfur-containing products. As a result the use of diethylamine was found to be also effective for the formation of pyridazines, and in the case of **1c** , the corresponding 4-methyl-3,6-di(4-pyridyl)pyridazine **8c**, (R'=Me) was obtained in 12% yield when tripropylamine was used. Haddadin *et al* . (4) reported that 3,6-diphenylpyridazine **7d** was obtained in 15% yield as the by-product in the synthesis of 1,2-diazocine from **1d** and cyclobutanone in refluxing diethylamine and in lower yield when **1d** was heated in triethylamine or diethylamine for a week. However, we were able to obtain **7d** in 74% as the best yield when sulfur was added to the mixture of **1d** and triethylamine in toluene. Furthermore, the expected sulfur-containing products, 2,5-diaryl-1,3,4-thiadiazoles, **11a** and **c**, were formed when morpholine was used as the base (Scheme 3 and runs 4 and 12 in Table 1). This reaction did not proceed in the absence of

amines. The best yield 53% for **11c** was observed when refluxed for 83 h using morpholine. Among the amines tested, butylamine also showed thiadiazole formation, but the yields were lower. Although the reason for the usefulness of morpholine as the amine in the formation of thiadiazoles is not clear, morpholine is knwon as the most popular amine in the preaparation of thioamides from ketones, sulfur and amines (Willgerodt-Kindler reaction) (14).



1 **9** **10** **11**

Scheme 3

Tetrazines **1b** and **1d** did not give the corresponding **11b** and **11d** in appreciable yields. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, a more reactive tetrazine than **1a-d**, gave only inseparable mixtures in all cases.

The formation of dihydrotetrazines **5a** and pyridazines **7** may be similarly explained as described by Haddadin *et al* . (4); nucleophilic attack by amines at the C-3 position of **1** (path a in Scheme 1) would give adducts **2**, whose nitrogen anion would abstract hydrogen from the ethyl group to give **3** with elimination of an iminium ion. The anion on **3** would further abstract hydrogen from the iminium ion to give dihydrotetrazines **5** with the formation of an enamine. Dihydrotetrazines **5b-d** are susceptible to air-oxidation to give tetrazines **1b-d**, while **5a** is relatively resistant to air-oxidation, giving **5a** as the product. 1,2,4,5-Tetrazines **1** would react with the enamines thus formed in an inverse electron demand Diels-Alder fashion to give **6**, which would extrude nitrogen and then aromatize to form pyridazines **7** (Scheme 2). Higher yields and / or a shorter reaction time due to the addition of sulfur to the reactants may be attributable to 1) the attack of the nucleophilic spcies "N" at **1** to form the adducts **4** followed by a loss of sulfur and iminium ion to give **3** (path b in Scheme 1); 2) the action of "N" as the base in the abstraction of the hydrogen in **2** . Another possibility is that sulfur may promote the dehydrogenation of **5** to **1** because of the well known oxidation ability of sulfur. However, it was ruled out by the experiment that reflux of the mixture of **5** and sulfur in toluene resulted in no appreciable increase in the yield or a shorter reaction time. The formation of 1,3,4-thiadiazoles **11** can be accounted for by intramolecular attack of the anion of **9** at the sulfur to give the bicyclic intermediates **10** followed by a loss of nitrogen to give **11** (Scheme 3).

Experimental

Melting points were determined using a MEL-TEMP II apparatus. The ir and mass spectra were recorded on a JASCO A-102 and a JEOL JMS DX-300 spectrometer, respectively. Elemental analyses were performed with a YANACO CHN-CODER MT-5. 1,2,4,5-Tetrazines **1a** (15), **b** (16), **c** (16), and **d** (17) were

prepared according to the literature methods.

General procedure

To a hot solution of **1** (1.0 mmol) and elemental sulfur (64 mg, 2.0 mmol) in toluene (40 ml), was added the amine (10 or 50 mmol) and then the mixture was refluxed. In case that a black tar was formed during the reaction, it was removed from the hot reaction mixture by decantation. After cooling, the precipitate was collected by filtration and recrystallized, or the residue after evaporation of the solvent *in vacuo* was separated by column chromatography on silica gel with an eluent of $CHCl_3$ or $CHCl_3$-MeOH. The reaction time and yields are shown in Table 1.

3,6-Di(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine **5a**: mp 189-191°C ; lit (15), mp 193-194°C.

3,6-Di(2-pyridyl)pyridazine **7a**: mp 175-176°C; lit (15), 179-180°C.

3,6-Di(3-pyridyl)pyridazine **7b**: mp 204-205°C. Ir (KBr): 1560, 1410, 1380, 1295 cm^{-1}; ms m/z (%): 234 (M^+, 100), 205 (8), 103 (97), 76 (32). Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.77; H, 4.31; N, 23.92. Found: C, 71.83; H, 4.46; N, 24.32.

3,6-Di(4-pyridyl)pyridazine **7c**: mp 253-255°C. Ir (KBr): 1600, 1570, 1560, 1410, 1300, 1220 cm^{-1}; ms m/z (%): 234 (M^+, 100), 206 (15), 103 (83), 76 (41). Anal. Calcd For $C_{14}H_{10}N_4$: C, 71.77; H, 4.31; N, 23.92. Found: C, 71.85; H, 4.41; N, 24.22.

3,6-Diphenylpyridazine **7d**

To a hot solution of **1d** (234 mg, 1.0 mmol) and sulfur (32 mg, 1.0 mmol) in toluene (15 ml), was added triethylamine (5.0 ml, 50 mmol). The mixture was refluxed for 48 h and treated as described above to give **7d** (171 mg, 74%), mp 221-223°C; lit. (17) mp 228-229°C.

4-Methyl-3,6-di(4-pyridyl)pyridazine **8c**: mp 271-272°C. Ir (KBr): 1585, 1560, 1540, 1400 cm^{-1}; ms m/z (%): 248 (M^+, 89), 247 (100), 117 (21), 90 (22); ^{1}H-nmr (CF_3COOD) : δ 2.80 (s, 3H), 8.61-9.23 (m, 9H). Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56: H, 4.87; N, 22.56. Found: C, 72.50; H, 5.01; N, 22.63.

2,5-Di(2-pyridyl)-1,3,4-thiadiazole **11a**: mp 217-218°C; lit. (18) mp 221-222°C.

2,5-Di(4-pyridyl)-1,3,4-thiadiazole **11c**

To a hot solution of **1c** (236 mg, 1.0 mmol) and sulfur (256 mg, 8.0 mmol) in toluene (30 ml), was added morpholine (1.0 ml, 11 mmol). The mixture was refluxed for 83 h. After cooling, the precipitate was collected by filtration and recrystallized from MeOH to give **11c** (128 mg, 53%), mp 233-235°C; lit. (19), mp 243°C.

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