Reaction of 4-Amino-1,2,4-triazines with Phosphorus Pentasulfide. Deamination During Aromatization

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Synthesis of several derivatives of thieno[2,3-*e*]-1,2,4-triazines has been achieved *via* the action of phosphorus pentasulfide on 6-vinyl- or 6-acylmethyl-5-oxo-1,2,4-triazine derivatives. During these investigations interesting synthetically useful functions for phosphorus pentasulfide in pyridine were observed, among which the deamination of certain *N*-amino heterocycles is unprecedented.

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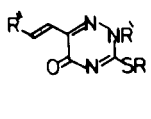
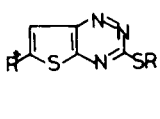
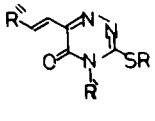
We recently reported an interesting synthesis of thiophenes condensed with heterocyclic nitrogen compounds from system like **2, 3** when acted upon with phosphorus pentasulfide in pyridine, where three reactions are accomplished in one step (thiation, cyclization and aromatization [1-4]). In an attempt to synthesize the possible bond isomers of thieno[2,3-*e*]-1,2,4-triazines **4, 5**, and **15-17** for theoretical and biological interest, we investigated the action of this reagent on the appropriate starting 6-vinyl-1,2,4-triazines **1, 6-10** [5].



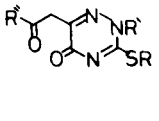
1, R = R' = H
2, R = CH_3; R' = H
3, R = H; R' = CH_3



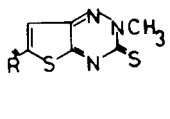
4, R = H
5, R = CH_3



6, R' = CH_3; R = H
7, R' = NH_2; R = H
8, R' = NH_2; R = CH_3
9, R' = N=CHPh; R = H
10, R' = N=CHPh; R = CH_3



11, R = R' = H
12, R = H; R' = CH_3
13, R = CH_3; R' = H



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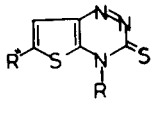
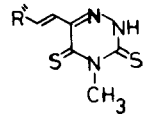


15, R = CH_3
16, R = NH_2
17, R = N=CHPh



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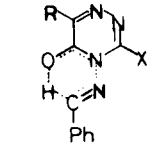

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a, R' = C_6H_5 b, R' = $C_6H_4OCH_3$-p c, R' = $C_6H_4CH_3$-p

Although compounds **3a-c** react with phosphorus pentasulfide in pyridine to give the corresponding thieno[2,3-*e*]-1,2,4-triazines **14a-c**, attempts to prepare the isomeric thienotriazines **15a-c** starting with **6a-c** under similar conditions, led only to thiation and the corresponding 3,5-dithioxotriazines **18a-c** were the sole reaction products [4].

In continuation to our attempts to prepare the 4-sustituted thienotriazines, we investigated the action of phosphorus pentasulfide on 6-β-arylvinyl-4-amino-3-mercapto-5-oxo-4,5-dihydro-1,2,4-triazines **7a-c** as a possible route towards the 4-aminothienotriazines **16a-c**. However, in this case we isolated the 3-mercaptothienotriazines **4a-c** but none of the expected **16a-c**. Clearly the formation of compounds **4a-c** involves removal of the 4-amino group. This led us to the study of the behavior of 6-β-arylvinyl-4-amino-3-methylmercapto-4,5-dihydro-1,2,4-triazines **8a-c** under the same conditions, in this case we found that the thienotriazines **4a-c** are the major reaction products together with the methyl derivatives **5a-c** in a ratio of about 4:1. Independent syntheses of the new thienotriazines **4a-c** are also successful by the action of phosphorus pentasulfide on compounds **1a-c** and also the appropriate 6-acylmethyltriazines **11**. Compounds **4a-c** are readily methylated with methyl iodide in basic medium to afford the methylmercapto derivatives **5a-c** identical with authentic samples prepared from each of compounds **2a-c** and **13a-c** [4].

The conversion of 4-amino derivatives **7, 8** into **4, 5** involves deamination of the 4-*N*-amino group and demethylation of the amidinyl thioethers. The latter reaction has been previously observed [6], however, the former has not, to the best of our knowledge, been previously reported. This interesting deamination could be explained by first formation of a condensation product with phosphorus pentasulfide which then possibly *via* a cyclic transition state undergoes facile deamination similar to the deamination reported with nitrous acid [7]. This is, also, similar to the deamination observed in our laboratory for the benzal derivatives **19** or upon heating the 4-aminotriazines with benzaldehyde at high temperature. The last deamination is proposed to proceed *via* a cyclic six centered aromatic transition state, the details of this study will be subject of a forthcoming publication. As a further support for this proposal is the fact that compounds **9a** and **10b** are readily converted into compounds **4a** and **5b** respectively upon treatment with phosphorus pentasulfide in pyridine. Compounds **9a** and **10b** required for this investigation were prepared by the condensation of benzaldehyde with compounds **7a** and **8b** respectively [9].

Table

Compounds [a]	Mp, °C	Yield % [b]	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N	S
4a	246	66 (A)	$C_{11}H_7N_3S_2$	53.85	2.87	17.13	26.14
		63 (B)	(245.32)	53.50	3.00	17.00	25.90
		60 (C)					
		35 (D)					
4b	275	65 (A)	$C_{12}H_9N_3S_2O$	52.34	3.29	15.26	23.29
		62 (C)	(275.34)	52.60	3.50	15.40	23.30
		30 (D)					
4c	276	75 (A)	$C_{12}H_9N_3S_2$	55.57	3.49	16.20	24.73
		69 (B)	(259.34)	55.70	3.70	16.30	24.80
		70 (C)					
		38 (D)					
5a	190 [4]	95 (F)	$C_{12}H_9N_3S_2$	—	—	—	—
		8 (D)	(259.34)	—	—	—	—
5b	202 [4]	91 (F)	$C_{13}H_{11}N_3S_2O$	—	—	—	—
		8 (D)	(289.37)	—	—	—	—
5c	178 [4]	93 (F)	$C_{13}H_{11}N_3S_2$	—	—	—	—
		10 (D)	(273.37)	—	—	—	—
11a	248 [11]	73 (A)	$C_{11}H_9N_3SO_2$	—	—	—	—
		85 (B)	(247.26)	—	—	—	—
11b	272	76 (A)	$C_{12}H_{11}N_3SO_3$	51.97	4.00	15.15	11.56
		60 (B)	(277.29)	51.70	4.30	14.90	11.40
11c	263	74 (A)	$C_{12}H_{11}N_3SO_2$	55.15	4.24	16.08	12.26
		70 (B)	(261.29)	55.40	4.40	15.80	11.90

[a] Compounds **4a**, ir (potassium bromide): 2600-3600 (w, br), 1560, 1530, 1480, 1440, 1365, 1235, 1205, 1125, 1090, 880, 770, 745 and 690 cm^{-1}; ms: m/e 245 (M^+); **4b**, ir (potassium bromide): 2600-3500 (w, br), 3220 (s), 1590, 1525, 1490, 1360, 1255, 1230, 1195, 1180, 1085 and 825 cm^{-1}; ms: m/e 275 (M^+); **4c** ir (potassium bromide): 2550-3500 (br), 1560, 1530, 1490, 1440, 1405, 1360, 1235, 1195, 1160, 1130, 1090, 810, 750 and 680 cm^{-1}; ms: m/e 259 (M^+); **5a**, ms: m/e 259; **5b**, nmr (deuteriochloroform): δ 2.75 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3) and 7.08-8.35 (m, 5H, Ar and thiophene H's) ppm; ms: m/e 289 (M^+); **5c**, nmr (deuteriochloroform): δ 2.4 (s, 3H, $ArCH_3$), 2.72 (s, 3H, SCH_3), 7.2-7.71 (m, 5H, Ar and thiophene H's) ppm; ms: m/e 273 (M^+); **11c**, ir (potassium bromide): 3270, 3040-3200 (br), 2950, 1700, 1670, 1610 and 1540 cm^{-1}. [b] A, B, C, D are the yields obtained from the experimental methods with the same notation. F is the report of yields of compounds **5** obtained by methylation of the corresponding **4**.

EXPERIMENTAL

All melting points are uncorrected. The pmr spectra were determined with a JEOL JNM-MH-100 with TMS as an internal standard. Mass spectra were recorded on Hitachi Perkin-Elmer RMS-4 spectrometer. Compounds prepared by different procedures were confirmed by mixed melting points and infrared spectra (potassium bromide) using a Unicam SP-1200 infrared spectrophotometer.

6-β-*p*-Tolylvinyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazine (**1c**).

This compound was prepared by the same procedure described by Semonsky *et al.* [8] for the preparation of compounds **1a,b**. *p*-Tolylidenepyruvic acid (19.0 g, 0.1 mole) and thiosemicarbazide (9.1 g, 0.1 mole) in water (48 ml) were heated under reflux for 5 minutes and then allowed to stand at room temperature for 2 hours whereby a yellowish precipitate was formed. This precipitate went into solution after addition of sodium hydroxide (8.4 g, 0.21 mole). The reaction mixture was then heated under reflux for 15 minutes and acidified with concentrated hydrochloric acid while being cooled in ice bath. The resulting precipitate was collected, washed with water and recrystallized from acetic acid to yield 23 g (94%) of **1c** as yellow needles, mp 276-278°; ir (potassium bromide): 1595 (w), 1610 (w), 1670 (s), 2600-3190 (w, br) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_3SO$: C, 58.75; H, 4.52; N, 17.13; S, 13.07. Found: C, 58.60; H, 4.60; N, 17.10; S, 12.90.

6-Acylmethyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines (**11a-c**).

Method A. From Aroylpyruvic Acid Ethyl Esters.

A mixture of the appropriate aroylpyruvic acid ethyl ester [10] (0.1 mole) and thiosemicarbazide (9.1 g, 0.1 mole) in water (20 ml) was heated under reflux for 5 minutes and left at ambient temperature for 2 hours, whereaby a yellowish precipitate was formed. This was dissolved by addition of a solution of sodium hydroxide (8.4 g, 0.21 mole) in water (28 ml), and then heated under reflux for 15 minutes. The reaction mixture was cooled in an ice bath and then acidified with concentrated hydrochloric acid. The resulting precipitate was collected, washed with water and recrystallized from ethanol into the corresponding derivatives **11a** (73%), **11b** (76%) and **11c** (74%) (see Table).

Method B. From Aroylpyruvic Acids, as Described for the Synthesis of **11a** [11].

To the appropriate aroylpyruvic acid (0.1 mole) in 1*N* sodium hydroxide (25 ml) was added thiosemicarbazide (9.1 g, 0.1 mole) in hot water (20 ml), and acetic acid (2 ml). The reaction mixture was then allowed to stand at room temperature overnight. The precipitated thiosemicarbazone was collected and heated under reflux in ethanol (50 ml) for 12 hours. After cooling, the precipitate was collected and recrystallized from ethanol into the corresponding derivatives **11a** (85%), **11b** (60%) and **11c** (70%) (see Table).

Thieno[2,3-*e*]-1,2,4-triazines (**4a-c**).

Method A. From **1a-c**.

A solution of each of **1a-c** [8] (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 6 hours. The precipitate obtained was collected, washed with water and recrystallized from dimethylformamide into the corrsponding products **4a-c** respectively (see Table).

Method B. From **7a-c**.

A solution of each of **7a-c** [9] (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 6 hours. After cooling, the precipitate was collected and recrystallized from dimethylformamide to yield **4a-c** respectively (see Table).

Method C. From **11a-c**.

Each of compounds **11a-c** (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 1-3 hours. After cooling the precipitate was collected, washed with water and recrystallized from dimethylformamide to give **4a-c** respectively (see Table).

Method D. From **8a-c**.

A mixture of each of **8a-c** [9] (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 6 hours. After cooling the precipitate was collected and washed with water. Dissolution in potassium hydroxide (5%, 20 ml), left a precipitate which was collected, washed with water and recrystallized from ethanol into **5a-c** respectively. The alkaline filtrate was acidified with concentrated hydrochloric acid to precipitate compounds **4a-c** respectively which were recrystallized from dimethylformamide (see Table).

Method E. From **9a**.

A solution of **9a** [9] (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 6 hours. After cooling, the precipitate was collected, washed with water and recrystallized from dimethylformamide to give 55% of **4a**.

Action of Phosphorus Pentasulfide on **10b**.

A solution of **10b** [9] (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (15 ml) was heated under reflux for 6 hours. After cooling the precipitate was collected, washed with water and recrystallized from ethanol to give 65% of **5b** [4].

Methylation of Compounds **4a-c**.

Each of compounds **4a-c** (0.01 mole) was dissolved in cold sodium methoxide solution (prepared from 0.23 g of sodium in 20 ml of anhydrous methanol) then methyl iodide (0.01 mole) was added. The reaction mixture was shaken for 30 minutes and left overnight at room temperature. The precipitate formed was collected and recrystallized from ethanol into compounds **5a-c** respectively (see Table) [4].

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[9] Compounds **7**, **8**, **9a**, **10b** and many derivatives of the general formula **19** have been synthesized according to the procedure cited in the Ph.D. thesis by M. A. Badawy, Cairo University (1980), and are now under publication together with a study of the thermal deamination of compounds **19** and its synthetic utility.

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