Synthesis of Thieno[2,3-*e*]-1,2,4-triazines

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3-Methylmercapto-5-oxo-6-vinyl- and 2-methyl-3-mercapto-5-oxo-6-vinyl-2,5-dihydro-1,2,4-triazines were readily converted into the corresponding thieno[2,3-*e*]-1,2,4-triazine in one step by the action of phosphorus pentasulfide in pyridine. 4-Methyl-3-mercapto-5-oxo-4,5-dihydro-1,2,4-triazine is only converted into the 5-thioxo analog and no thiophene ring product was obtained under the same conditions. Thieno[2,3-*e*]-1,2,4-triazines were also more efficiently obtained by the action of phosphorus petnasulfide in pyridine on the appropriate 6-acylmethyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazine.

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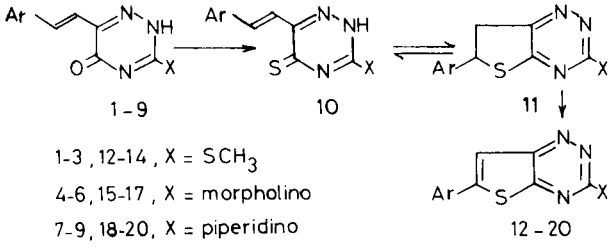
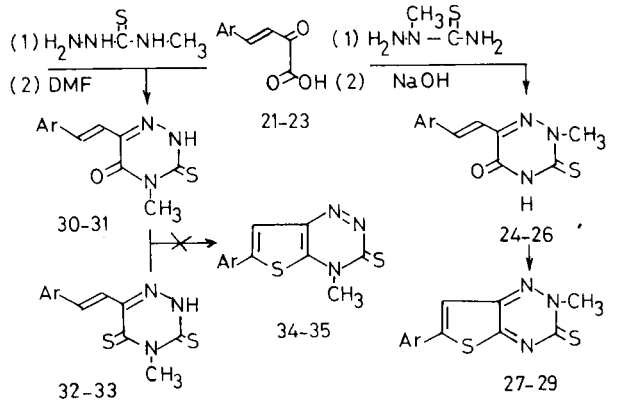
Condensed 1,2,4-triazines with other heterocyclic nuclei are interesting from both theoretical as well as the biological point of view. Thieno[2,3-*e*]-1,2,4-triazines are, to the best of our knowledge (1) members of an unknown ring system, and only a preliminary communication from this laboratory described one interesting synthetic approach towards such a ring system (2).

Our first proposed scheme starts with derivatives of 6-vinyl-5-oxo-2,5-dihydro-1,2,4-triazines (**1-9**) (3) which are expected to undergo thiation to the 5-thioxo- derivatives (**10**) (4,5) or the ring tautomer (**11**) and the latter can be oxidized to **12-20**.



All these processes were now found to take place in a one step reaction by the action of phosphorus pentasulfide in pyridine on compounds **1-9**. Thus 6-β-arylvinyl-3-methylmercapto-, 3-morpholino- and 3-piperidino-5-oxo-2,5-dihydro-1,2,4-triazines **1-9** yield the respective thieno[2,3-*e*]-1,2,4-triazines **12-20**. The structure of compounds **12-20** was confirmed by analytical and spectral data. Alternatively the morpholino- and piperidinothieno-[2,3-*e*]-1,2,4-triazines **15-20** were also obtained in excellent yields from the methylmercaptothieno[2,3-*e*]-1,2,4-triazines **12-14** by refluxing in morpholine and piperidine, respectively for 6 hours.

We also investigated the action of phosphorus pentasulfide in pyridine on 6-β-arylvinyl-2-methyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines **24-26**. These were found to yield the corresponding thieno[2,3-*e*]-1,2,4-triazines (**27-29**). Compounds **27-29** showed the correct analytical and spectral data.



The starting triazines **24-26** were obtained by condensing the appropriate arylidinepyruvic acid **21-23** (6) with 2-methylthiosemicarbazide (7) to the thiosemicarbazone followed by cyclization with 2.1 equivalents aqueous sodium hydroxide upon heating for a short time.

The isomeric 4-methyl derivatives **30-31** were obtained by the condensation of **21-22** with 4-methylthiosemicarbazide (8) followed by cyclization by refluxing in dimethylformamide. Treatment of compounds **30-31** with phosphorus pentasulfide in pyridine yielded only the 3,5-dithioxo-1,2,4-triazines **32-33** (which give the correct molecular ion peak in mass spectra) and none of the expected thieno[2,3-*e*]-1,2,4-triazines **34-35**.

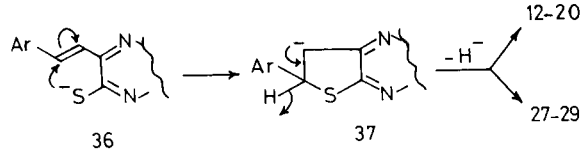
The most upsetting point in the above synthesis is that the yield was not very satisfactory in most cases. It was found that the best yield of thieno[2,3-*e*]-1,2,4-triazines could be obtained by heating under reflux for 6 hours the starting traizines with phosphorus pentasulfide in a 1:2 molar ratio in pyridine. This could be predicted from the proposed mechanism for the formation of compounds **12-20** and **27-29** from **1-9** and **24-26** which starts with the formation of the 5-mercapto anion **36** (in pyridine medium) which undergoes a Michael type addition to the activated vinyl group yielding intermediate **37**. The latter undergoes hydride ion elimination to the final products **12-20** and **27-29**.

Table

Products (a)	Ar (b)	Mp °C	Yield % (c)	Formula (Molecular Weight)	Analysis % (d) Calcd./Found C	H	N	S
12	A	190 (2)	30 (i)	$C_{12}H_9N_3S_2$	—	—	—	—
			80 (ii)	(259.34)				
13	B	178	33 (i)	$C_{13}H_{11}N_3S_2$	57.11	4.05	15.37	23.45
			68 (ii)	(273.37)	57.40	4.20	15.70	23.10
14	D	202	37 (i)	$C_{13}H_{11}N_3S_2O$	53.95	3.83	14.52	22.16
			69 (ii)	(289.37)	54.30	3.80	14.40	22.20
15	A	192 (2)	35 (i)	$C_{15}H_{14}N_4SO$	—	—	—	—
			82 (iii)	(298.35)				
16	B	185	32 (i)	$C_{16}H_{16}N_4SO$	61.51	5.16	17.93	10.26
			74 (iii)	(312.38)	61.80	4.80	18.10	9.90
17	D	195	40 (i)	$C_{16}H_{16}N_4SO_2$	58.52	4.91	17.06	9.76
			94 (iii)	(328.38)	58.30	5.00	16.90	9.80
18	A	155	36 (i)	$C_{16}H_{16}N_4S$	64.83	5.44	18.90	10.82
			90 (iii)	(296.38)	65.00	5.30	18.70	11.10
19	B	175	35 (i)	$C_{17}H_{18}N_4S$	65.76	5.84	18.05	10.33
			75 (iii)	(310.40)	65.70	5.60	18.20	10.30
20	D	154	37 (i)	$C_{17}H_{18}N_4SO$	62.56	5.55	17.16	9.82
			53 (iii)	(326.40)	62.80	5.40	16.90	10.00
24	A	231	73	$C_{12}H_{11}N_3SO$	58.75	4.52	17.13	13.07
				(245.29)	58.80	4.70	17.30	13.30
25	C	251	98	$C_{12}H_{10}ClN_3SO$	51.52	3.60	15.02	11.46
				(279.73)	51.40	3.50	15.20	11.30
26	D	239	78	$C_{13}H_{13}N_3SO_2$	56.71	4.76	15.26	11.64
				(275.31)	56.50	4.70	15.40	11.50
27	A	300	69 (i)	$C_{12}H_9N_3S_2$	55.57	3.49	16.20	24.73
			85 (ii)	(259.34)	55.90	3.50	16.10	24.70
28	C	287	85 (i)	$C_{12}H_8ClN_3S_2$	49.06	2.74	14.30	21.82
			86 (ii)	(293.78)	49.00	2.90	14.50	21.70
29	D	264	73 (i)	$C_{13}H_{11}N_3S_2O$	53.95	3.83	14.52	22.16
			85 (ii)	(289.37)	54.00	3.90	14.60	21.90
30	A	244	83	$C_{12}H_{11}N_3SO$	58.75	4.52	17.13	13.07
				(245.29)	59.10	4.70	17.50	13.00
31	D	228	85	$C_{13}H_{13}N_3SO_2$	56.71	4.76	15.26	11.64
				(275.31)	56.70	4.90	15.30	11.80
32	A	218	70	$C_{12}H_{11}N_3S_2$	55.14	4.24	16.07	24.53
				(261.36)	54.80	4.40	16.30	24.70
33	D	209	83	$C_{13}H_{13}N_3S_2O$	53.58	4.49	14.42	22.00
				(291.38)	53.70	4.80	13.90	22.30
41	B	234	54	$C_{13}H_{13}N_3SO_2$	56.71	4.75	15.26	11.64
				(275.31)	56.40	4.90	15.20	11.50
42	D	213	41	$C_{13}H_{13}N_3SO_3$	53.59	4.50	14.42	11.00
				(291.31)	53.60	4.40	14.10	11.30
43	A	212	45	$C_{12}H_{11}N_3SO_2$	55.16	4.24	16.08	12.27
				(261.29)	55.40	4.00	16.20	12.00
44	C	210	48	$C_{12}H_{10}ClN_3SO_2$	48.73	3.41	14.20	10.84
				(295.73)	49.00	3.20	14.30	10.90
45	D	185	55	$C_{13}H_{13}N_3SO_3$	53.59	4.50	14.42	11.00
				(291.31)	53.80	4.30	14.50	10.80

(a) Compounds **13**, nmr (deuteriochloroform): δ 2.4 (s, 3H, $ArCH_3$), 2.72 (s, 3H, SCH_3), 7.00-7.71 (m, 5H, Ar and thiophene H's), ppm; **27**, nmr (Dioxane-d_8): δ 3.95 (s, 3H, NCH_3) and 7.0-7.7 (m, 6H, Ar and thiophene H's) ppm; ms: m/e 259 (M^+); **32**, ms: m/e 261 (M^+); **41**, nmr (DMSO-d_6): δ 2.5 (s, 3H, SCH_3), 4.26 (s, 2H, CH_2), 6.4 (s, 1H, NH) and 7.4-8.0 (m, 5H, ArH's) ppm; **43**, nmr (DMSO-d_6): δ 3.25 (s, 1H, NH), 3.71 (s, 3H, NCH_3), 4.25 (s, 2H, CH_2) and 7.4-7.95 (m, 5H, ArH's) ppm; **44**, nmr (DMSO-d_6): δ 3.3 (s, 1H, NH), 3.73 (s, 3H, NCH_3), 4.28 (s, 2H, CH_2), 7.5-7.97 (m, 4H, ArH's) ppm; **45**, nmr (DMSO-d_6): δ 3.2 (s, 1H, NH), 3.75 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), and 6.95, 7.8 (two doublets, 4H, J = 8 cps, ArH's) ppm. (b) A = C_6H_5; B = $C_6H_4CH_3$-*p*; C = C_6H_4Cl-*p*; D = $C_6H_4OCH_3$-*p*. (c) These yields are from the action of (i) phosphorus pentasulfide on 6-vinyltriazines **1-9**, **24-26**, (ii) phosphorus pentasulfide on 6-aroylmethyltriazines **41-45** and (iii) piperidine and/or morpholine on 3-methylmercaptothieno[2,3-*e*]-1,2,4-triazines **12-14**. (d) Compounds **25**: Cl, Calcd: 12.67. Found: 12.40; **28**: Cl, Calcd: 12.06. Found: 12.00; **44**: Cl, Calcd: 11.98. Found: 12.30.

The hydride ion elimination seems to be facilitated by the use of the excess pentavalent phosphorus (P_2S_5) which probably oxidizes it into hydrogen sulfide.



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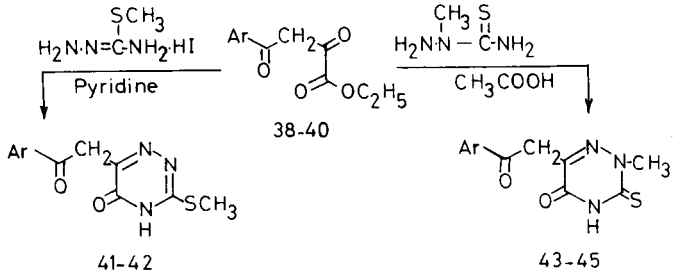
Another more efficient route for the synthesis of thieno-[2,3-*e*]-1,2,4-triazines **12-14** and **27-29** was investigated. This starts by condensing aroylpyruvic acid ethyl esters **38-40** (9) with *S*-methylisothiosemicarbazide hydroiodide (10) and 2-methylthiosemicarbazide to the respective new 6-acylmethyltriazine derivatives **41-42** and **43-45**. Treatment of the latter compounds with phosphorus pentasulfide in pyridine gave compounds **12-14** and **27-29** in good yields (70-85%). Analytical and spectral data of compounds **41-42** and **43-45** are consistent with their structures.



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 identity of infrared spectra (potassium bromide) using a Unicam SP 1200 infrared spectrophotometer.

2-Methyl-6-β-arylvinyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (**24-26**).

A mixture of the appropriate arylidinepyruvic acid (**21-23**) (0.01 mole) and 2-methylthiosemicarbazade (0.01 mole) in water (20 ml) was boiled for 5 minutes, then left at ambient temperature for 2 hours and the precipitated 2-methylthiosemicarbazone was collected. This thiosemicarbazone was heated under reflux for 15 minutes in aqueous sodium hydroxide solution (1*N*, 2.1 equivalents), cooled and acidified with concentrated hydrochloric acid. The precipitate formed was collected and recrystallized from DMF into crystals of compounds **24-26** (Table).

4-Methyl-6-β-arylvinyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (**30-31**).

Arylidinepyruvic acid 4-methylthiosemicarbazones were obtained exactly as described in the previous experiment using 4-methylthiosemicarbazide. Cyclization of these thiosemicarbazones (0.01 mole) was achieved by heating under reflux in DMF (10 ml) for 3 hours. The crystals precipitated upon cooling were collected and recrystallized from DMF into the corresponding 4-methyltriazines **30-31** (Table).

4-Methyl-6-β-arylvinyl-3,5-dithioxo-2,3,4,5-tetrahydro-1,2,4-triazines (**32-33**).

A solution of each of compounds **30-31** (0.01 mole) and phosphorus pentasulfide (0.015 mole) in pyridine (20 ml) was heated under reflux for 6 hours, cooled and diluted with water. The obtained precipitate was then filtered off, dried and recrystallized from butanol into compounds **32-33** (Table).

6-Acylmethyl-3-methylmercapto-5-oxo-2,5-dihydro-1,2,4-triazines (**41-42**).

A mixture of *S*-methylisothiosemicarbazide hydroiodide (0.01 mole) and the appropriate aroylpyruvic ester **38-39** (0.01 mole) in dry pyridine (10 ml) was heated under reflux for 1 hour, cooled and the precipitate was collected and crystallized from ethanol into compounds **41-42** (Table).

2-Methyl-6-acylmethyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (**43-45**).

The appropriate ester **38-40** (0.01 mole) in acetic acid (25 ml) was added to a solution of 2-methylthiosemicarbazide (0.01 mole) in boiling water (10 ml) and then heated under reflux for 15 minutes during which a crystalline precipitate began to separate. The product obtained upon cooling was recrystallized from acetic acid into compounds **43-45** (Table).

Thieno[2,3-*e*]-1,2,4-triazines (**12-20**) and (**27-29**).

A solution of each of **1-9, 24-26, 41-42** and **43-45** (0.01 mole) and phosphorus pentasulfide (0.02 mole) in pyridine (20 ml) was heated under reflux for 6 hours. The product obtained upon cooling was collected, washed with water then alcohol and finally crystallized from dimethylformamide (Table).

3-Morpholino (and 3-piperidino)thieno[2,3-*e*]-1,2,4-triazines (**15-20**).

A solution of the appropriate thieno[2,3-*e*]-1,2,4-triazine **12-14** (0.5 g) in morpholine and/or pipieridine (3 ml) was heated under reflux for 6 hours, cooled and the precipitate was collected and recrystallized from dimethylformamide (Table).

REFERENCES AND NOTES

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(3) Compounds **1-9** were prepared according to the procedures cited in literature (1).

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