Studies on the Synthesis of 2-(2-Arylvinyl)thieno[2,3-*d*]pyrimidines and 5-(2-Arylvinyl)triazolothieno[3,2-*e*]pyrimidines

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Synthesis of 2-(2-arylvinyl)thienopyrimidines, by the acid catalyzed condensation of nitriles with thiophene *o*-aminocarbonyl compounds, the condensation of aldehydes with thiophene *o*-aminoamides, the base catalyzed condensation of aldehydes with 2-methylthienopyrimidines and by the Wittig condensation of 2-thienopyrimidinylmethylphosphonium salts with aldehydes is described. Isomeric 5-methyltriazolothienopyrimidines were found to react, under basic condition, with aldehydes yielding 5-(2-arylvinyl)triazolo[2,3-*c*]thienopyrimidines. While 5-styryltriazolo[4,3-*c*] isomers resisted acid catalysed isomerization, they were found to isomerize to triazolo[2,3-*c*]pyrimidines under base catalysis.

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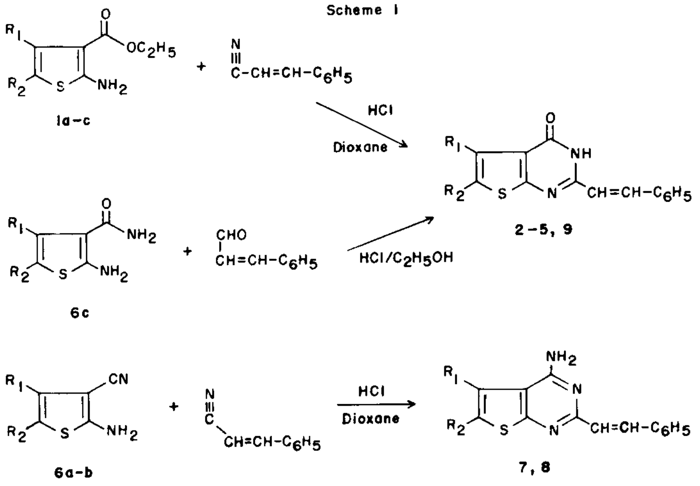
The synthesis of arylvinyl heterocycles has attracted the attention of medicinal chemists because of their potential pharmacodynamic properties. Numerous publications have appeared describing the synthesis of arylvinyl substituted condensed pyrimidines possessing a variety of pharmacological activities, such as anticonvulsant [2], antiinflammatory [3], bactericidal [4], fungicidal [5] and antifertility activities [6]. Herein, we report the synthesis of arylvinyl derivatives of thienopyrimidines and triazolothienopyrimidines by different routes.

The acid catalysed condensation of nitriles with *o*-aminocarbonyl compounds has been found to be a general method of synthesis of condensed pyrimidines [7]. The reaction of cinnamonitrile with *o*-aminoesters **1a-c** and *o*-aminonitriles **6a,b** in the presence of dry hydrogen chloride gas, in dioxane, yielded the corresponding 2-styrylthienopyrimidines **2-5** and **7, 8** (Scheme I, Tables I and II, Method A).

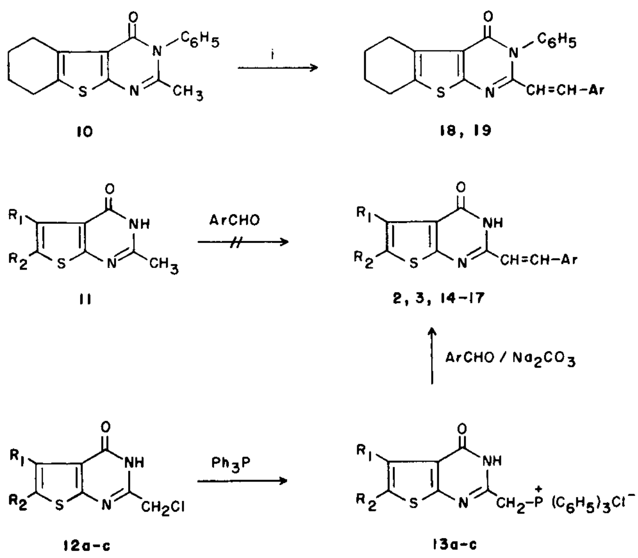
Scheme I



The reaction of cinnamaldehyde with the thiophene *o*-aminoamides **6c** in absolute ethanol in the presence of aqueous hydrochloric acid yielded directly the 2-styrylthienopyrimidines **2, 9** (Table I, Method B).

3-Arylsubstituted 2-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **10** could be condensed with aromatic aldehydes, in the presence of sodium ethoxide in ethanol, to obtain the corresponding 2-(2-arylvinyl) derivatives **18, 19** (Table III, Method C). However, attempts to react 2-methylthieno[2,3-*d*]pyrimidines **11** with aldehydes in the presence of either acidic or basic catalysts led only to the recovery of starting materials. Therefore, the Wittig reaction of 2-thienopyrimidinylmethylphosphonium chlorides with aldehydes was attempted as an alternative approach for the synthesis of 3-unsubstituted-2-(2-arylvinyl)thieno[2,3-*d*]pyrimidines. The desired phosphonium chlorides **13a-c** were prepared by reacting triphenylphosphine with the readily accessible 2-chloromethylthienopyrimidines **12a-c** [8] in refluxing toluene or xylene. The salts thus obtained could, successfully, be condensed with aromatic aldehydes employing a mild base such as sodium carbonate in methanol (Scheme II, Table I, Method D).

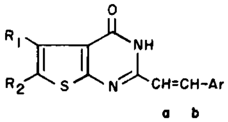
Scheme II



i = ArCHO/NaOC$_2$H$_5$ in C$_2$H$_5$OH.

Table I

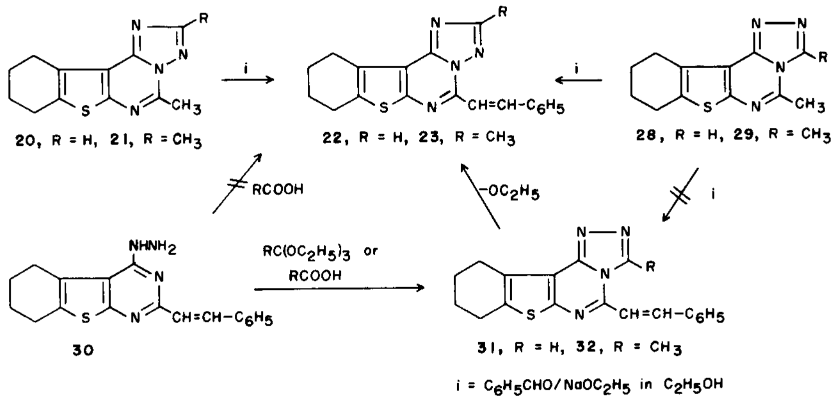
2-(2-Arylvinyl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones



Compound No.	R_1	R_2	Ar	Method	Mp °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
2	$-(CH_2)_4-$		C_6H_5	A	315-317	58	E-Ch	$C_{18}H_{16}N_2OS$	308	70.10	5.23
										70.05	5.51
	$-(CH_2)_4-$		C_6H_5	D	314-316	78	E-Ch	$C_{18}H_{16}N_2OS$	308 [d]	70.10	5.23
	$-(CH_2)_4-$		C_6H_5	B	315-317	46	E-Ch	$C_{18}H_{16}N_2OS$	308	70.22	5.61
3	CH_3	CH_3	C_6H_5	A	295-297	39	E-Ch	$C_{16}H_{14}N_2OS$	282	68.06	5.00
										67.96	5.24
	CH_3	CH_3	C_6H_5	D	296-298	85	E-Ch	$C_{16}H_{14}N_2OS$	282	68.06	5.00
										68.15	5.22
4	CH_3	$COOC_2H_5$	C_6H_5	A	278-280	74	A	$C_{18}H_{16}N_2O_3S$	340	63.51	4.74
										63.77	5.10
5	H	C_2H_5	C_6H_5	A	232-234	54	B	$C_{16}H_{14}N_2OS$	282	68.06	5.00
										68.33	5.01
9	$-(CH_2)_2-N(CH_2C_6H_5)-CH_2-$		C_6H_5	B	191-193	38	E	$C_{24}H_{21}N_3OS$	399 [d]	72.15	5.30
										71.95	5.65
14	$-(CH_2)_4-$		$4-NO_2C_6H_4$	D	272-274	68	E-Ch	$C_{18}H_{15}N_3O_3S$	353	61.17	4.28
										60.80	4.54
15	$-(CH_2)_4-$		$4-CH_3OC_6H_4$	D	323-325	71	E-Ch	$C_{19}H_{18}N_2O_2S$	338	67.43	5.36
										67.62	5.80
16	$-(CH_2)_4-$		$3,4,5-(CH_3O)_3-C_6H_2$	D	279-281	55	D	$C_{21}H_{22}N_2O_4S$	398	63.30	5.57
										63.29	5.60
17	C_6H_5	H	$4-NO_2C_6H_4$	D	>330	85	D	$C_{20}H_{13}N_3O_3S$	375	64.00	3.49
										64.47	3.80

[c] A = Acetic acid, B = Benzene, Ch = Chloroform, D = Dioxane, E = Ethanol. [d] Molecular weight determined by mass spectra.

Scheme III

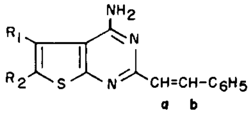


Triazolothienopyrimidines are analogous to 3-phenylthienopyrimidin-4-ones in that they lack an acidic proton in the pyrimidine nucleus and hence, might be expected to undergo the condensation reaction with aldehydes under basic conditions. In fact, the reaction of benzaldehyde with 5-methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines **20, 21** in the presence of sodium ethoxide in ethanol did yield the corresponding 5-styryl-1,2,4-triazolo[2,3-*c*]thienopyrimidines **22, 23**. The compounds **24-27** were similarly prepared from the corresponding 5-methyltriazolothienopyrimidines (Table IV, Method C).

Interestingly, it was found that the base catalysed condensation of benzaldehyde with 5-methyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines **28, 29** yielded products

Table II

4-Amino-2-styrylthieno[2,3-*d*]pyrimidines

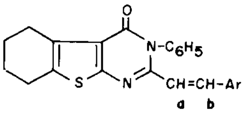


Compound No.	R_1	R_2	Method	Mp °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
7	$-(CH_2)_4-$		A	241-243	36	D	$C_{18}H_{17}N_3S$	307 [d]	70.32 70.10	5.57 5.86
8	CH_3	CH_3	A	232-234	35	B	$C_{16}H_{15}N_3S$	281	68.30 68.31	5.37 5.76

[c] B = Benzene, D = Dioxane. [d] Molecular weight determined by mass spectra.

Table III

2-(2-Arylvinyl)-3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones



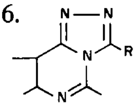
Compound No.	Ar	Method	Mp °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
18	C_6H_5	C	209-211	44	PE-B	$C_{24}H_{20}N_2OS$	384 [d]	74.97 74.83	5.24 5.48
19	$4\text{-}NO_2C_6H_4$	C	233-235	42	PE	$C_{24}H_{19}N_3O_3S$	429	67.11 66.76	4.46 4.59

[c] B = Benzene, PE = Petroleum Ether (60-80). [d] Molecular weight determined by mass spectra.

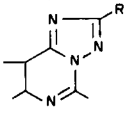
which were found to be identical with **22**, **23**, indicating thereby the occurrence of isomerization during the course of the condensation. However, the synthesis of isomeric triazolopyrimidines **31**, **32** could be achieved through the cyclization of 4-hydrazino-2-styrylthieno[2,3-*d*]pyrimidine **30** with orthoesters (Table V). These triazoles **31**, **32**, indeed, were found to undergo isomerization to **22**, **23** on treatment with a catalytic amount of sodium ethoxide in ethanol (Scheme III).

Further, it is of interest to note that the cyclization of 4-hydrazino-2-styrylthienopyrimidine **30** with formic acid or acetic acid at reflux temperature also yielded the 5-styryl-1,2,4-triazolo[4,3-*c*] isomers **31** or **32**, instead of the normally expected [2,3-*c*] isomers **22** or **23** [9]. The triazoles **31** and **32** also resisted isomerization to **22** and **23**, respectively, under acidic conditions such as formic acid at reflux or *p*-toluenesulfonic acid in refluxing benzene. Apparently, the styryl substituent at the 5-position in the triazolo[4,3-*c*]thienopyrimidines makes them resistant towards acid catalysed isomerization.

In accordance with the general observation [9] that the triazolo[4,3-*c*]thienopyrimidines of the structure **33** exhibit a more downfield signal for the substituent R than that of the [2,3-*c*] isomers of the structure **34**, it was found that the triazole proton signal of **31** appears at δ 9.0, while that of **22** appears at δ 8.3. Similarly, the -CH_3 signal of [4,3-*c*] isomer **32** appears at δ 3.0 while that of [2,3-*c*] isomer **23** appears at δ 2.6.



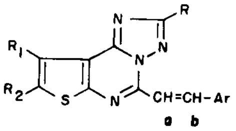
33



34

Table IV

5-(2-Arylvinyl)-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines

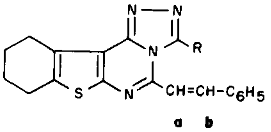


Compound No.	R_1	R_2	R	Ar	Method	Mp °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
22	$-(CH_2)_4-$		H	C_6H_5	C	250-252	60	E-Ch	$C_{19}H_{16}N_4S$	332	68.65 68.41	4.85 5.02
23	$-(CH_2)_4-$		CH_3	C_6H_5	C	219-221	78	D	$C_{20}H_{18}N_4S$	346	69.33 69.57	5.24 5.46
24	$-(CH_2)_4-$		H	$4\text{-}NO_2C_6H_4$	C	264-266	48	E-Ch	$C_{19}H_{15}N_5O_2S$	377	60.46 60.40	4.01 4.25
25	$-(CH_2)_4-$		H	$4\text{-}CH_3OC_6H_4$	C	218-220	55	E-Ch	$C_{20}H_{18}N_4OS$	362	66.27 66.30	5.01 5.25
26	CH_3	CH_3	H	C_6H_5	C	169-171	49	E-Ch	$C_{17}H_{14}N_4S$	306	66.64 66.46	4.61 4.88
27	CH_3	CH_3	H	2-thienyl	C	193-195	64	E-Ch	$C_{15}H_{12}N_4S_2$	312 [d]	57.66 57.49	3.87 4.26

[c] Ch = Chloroform, D = Dioxane, E = Ethanol. [d] Molecular weight determined by mass spectra.

Table V

5-Styryl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines



Compound No.	R	Mp °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
31	H	242-243	66	E	$C_{19}H_{16}N_4S$	332 [d]	68.65 68.41	4.65 5.30
32	CH_3	210-212	81	E-Ch	$C_{20}H_{18}N_4S$	346 [d]	69.33 69.67	5.24 5.60

[c] Ch = Chloroform, E = Ethanol. [d] Molecular weight determined by mass spectra.

All the compounds synthesised were characterized by their elemental analysis and spectral data (Table VI).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded in nujol mulls or potassium bromide on a Perkin-Elmer 337 Grating spectrophotometer. The nmr spectra were taken on a Varian A-60 spectrometer. Mass spectra were obtained on a Varian Atlas CH-7 mass spectrophotometer at 70 eV ionising beam, using direct insertion probe.

Method A. Preparation of 2-Styrylthieno[2,3-*d*]pyrimidines by the Condensation of Thiophene *o*-Aminoesters or Nitriles with Cinnamonitrile **2-5**, **7** and **8**.

A stream of dry hydrogen chloride gas was passed through a mixture of thiophene *o*-aminoester or nitrile (0.01 mole) and cinnamonitrile (1.41 g, 0.011 mole) in dioxane (20 ml) for 5 hours. The reaction mixture was allowed to stand overnight at room temperature, poured into ice-water

Table VI

Spectral Data

Compound No.	IR cm^{-1} (Nujol or Potassium Bromide)	MS: m/e	^1H NMR (Deuteriochloroform or DMSO-d_6/TMS) δ ppm [e]
2	1660 (C=O), 975 (CH=CH, *trans*)	308 (M^+), 293, 280, 267, 251, 236	—
3	1660 (C=O), 980 (CH=CH, *trans*)	—	2.41 (3H, s, CH_3 at C_5), 3.3 (3H, s, CH_3 at C_6), 7.53 (5H, m, Ar-*H*), 8.08 (1*H*, d, *H*a, J = 14 Hz), 6.91 (1H, d, *H*b, J = 14 Hz)
4	1720, 1680 (C=O), 980 (CH=CH, *trans*)	—	—
5	1670 (C=O), 970 (CH=CH, *trans*)	—	—
7	3370, 3300, 3170 (NH_2), 970 (CH=CH, *trans*)	307 (M^+), 291, 278, 262, 252, 246, 230	—
8	3400, 3310, 3200 (NH_2), 975 (CH=CH, *trans*)	—	—
9	1660 (C=O), 980 (CH=CH, *trans*)	399 (M^+), 370, 322, 280, 267, 251, 237	—
14	1660 (C=O), 1580, 1390 (NO_2), 970 (CH=CH, *trans*)	—	—
15	1680 (C=O), 980 (CH=CH, *trans*)	—	—
16	1660 (C=O), 970 (CH=CH, *trans*)	—	—
17	1660 (C=O), 1585, 1395 (NO_2), 970 (CH=CH, *trans*)	—	—
18	1670 (C=O), 960 (CH=CH, *trans*)	384 (M^+), 369, 355, 307, 293, 279, 206	1.87 (4H, m, CH_2 at 6 and 7), 2.92 (4H, m, CH_2 at 5 and 8), 7.44 (10H, m, Ar-*H*), 7.87 (1H, d, *H*a, J = 15.6 Hz), 6.34 (1H, d, *H*b, J = 15.6 Hz)
19	1675 (C=O), 1590, 1340 (NO_2), 970 (CH=CH, *trans*)	—	—
22	970 (CH=CH, *trans*)	—	—
23	975 (CH=CH, *trans*)	—	1.9 (4H, m, CH_2 at 9 and 10), 2.61 (3H, s, triazole CH_3), 2.95 (4H, m, CH_2 at 8 and 11), 7.43 (5H, m, Ar-*H*), 8.16 (1H, d, *H*a, J = 14 Hz), 7.77 (1H, d, *H*b, J = 14 Hz)
24	1580, 1380 (NO_2), 970 (CH=CH, *trans*)	—	—
25	975 (CH=CH, *trans*)	—	—
26	975 (CH=CH, *trans*)	—	—
27	975 (CH=CH, *trans*)	312 (M^+), 297, 284, 279, 258, 252, 240	—
31	975 (CH=CH, *trans*)	332 (M^+), 317, 304, 282, 267, 251, 249	2.0 (4H, m, CH_2 at 9 and 10), 3.03 (4H, m, CH_2 at 8 and 11), 8.13 (1H, d, *H*a, J = 16 Hz), 7.2 (1H, d, *H*b, J = 16 Hz), 7.5 (5H, m, Ar-*H*), 9.03 (1H, s, triazole proton)
32	975 (CH=CH, *trans*)	346 (M^+), 331, 318, 304, 291, 276, 269, 251	1.93 (4H, m, CH_2 at 9 and 10), 3.0 (7H, m, CH_2 at 8 and 11 and triazole CH_3), 7.86 (1H, d, *H*a, J = 14 Hz), 7.4 (1H, d, *H*b, J = 14 Hz), 7.3 (5H, m, Ar-*H*)

[e] Line shapes: s = singlet, d = doublet, m = multiplet.

and basified with 10% ammonium hydroxide solution. The precipitate obtained was filtered, washed with water and dried. Crystallization from a suitable solvent yielded the corresponding 2-styrylthienopyrimidine.

Method B. Preparation of 2-Styrylthieno[2,3-*d*]pyrimidines by the Condensation of *o*-Aminoamides with Cinnamaldehyde **2**, **9**.

A mixture of thiophene *o*-aminoamide (0.01 mole) and cinnamaldehyde (1.45 g, 0.011 mole) in absolute ethanol (50 ml) was treated with concentrated hydrochloric acid (0.5 ml) and refluxed for 5 hours. Ethanol was removed by distillation under vacuum. The solid obtained was washed with saturated sodium bicarbonate solution and water and dried. Crystallization from a suitable solvent yielded the corresponding 2-styrylthieno[2,3-*d*]pyrimidines.

Method C. Base Catalysed Condensation of 2-Methyl-3-phenylthieno[2,3-*d*]pyrimidines and 5-Methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines with Aldehydes **18**, **19** and **22-27**.

A mixture of 2-methyl-3-phenylthieno[2,3-*d*]pyrimidine or 5-methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine (0.01 mole), appropriate aldehyde (0.011 mole) and sodium ethoxide (0.75 g, 0.011 mole) in absolute ethanol (50 ml) was warmed on a water bath at 50-60° for 15-20 minutes and allowed to stand at room temperature for 12 hours. The solid separated was filtered and dried. Crystallization from a suitable solvent yielded the corresponding 2-arylvinylthienopyrimidines.

Method D. Preparation of 2-(2-Arylvinyl)thieno[2,3-*d*]pyrimidines by the Condensation of Thienopyrimidinylmethylphosphonium Chloride with Aldehydes **2**, **3** and **14-17**.

A mixture of 2-chloromethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (0.01 mole) and triphenylphosphine (2.61 g, 0.01 mole) in toluene or xylene (50 ml) was refluxed for 7-8 hours. Yellow crystalline mass obtained on cooling the reaction mixture was used without purification for the condensation with aldehydes.

To a solution of triphenylphosphonium chloride (0.005 mole) and an appropriate aldehyde (0.0025 mole) in methanol (25 ml) was added dropwise 10% aqueous sodium carbonate solution (4 ml). The yellow precipitate obtained was filtered, washed with methanol, dried and crystallized from a suitable solvent.

Preparation of 4-Chloro-2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine.

Phosphorous oxychloride (10 ml) was added to a cooled suspension of 2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (3.08 g, 0.01 mole) in dimethylformamide (30 ml) and stirred at 0-5° for 15-20 minutes. After standing at room temperature for 12 hours, the mixture was poured into crushed ice and neutralized with sodium bicarbonate. The solid obtained was filtered, washed with water and dried. Crystallization from petroleum ether-benzene mixture gave a yellow crystalline compound, mp 138-140°, yield 2.5 g (77%); ir (nujol): 980 cm^{-1} (-CH=CH, *trans*).

Anal. Calcd. for $C_{18}H_{15}ClN_2S$ (326.83): C, 66.14; H, 4.63. Found: C, 66.40; H, 4.99.

Preparation of 4-Hydrazino-2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidine (**30**).

To a warm solution of 4-chloro-2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (3.26 g, 0.01 mole) in 15 ml of ethanol was added a solution of hydrazine hydrate (99%, 5 ml) in ethanol (5 ml), dropwise. The mixture was refluxed for 2 hours and cooled. The solid obtained was filtered, washed and dried. Crystallization from ethanol yielded yellow solid, mp 208-210°, yield 2.0 g (62%); ir (potassium bromide): 3300 (NH_2), 965 cm^{-1} (CH=CH, *trans*).

Anal. Calcd. for $C_{18}H_{18}N_4S$ (322.42): C, 67.05; H, 5.63. Found: C, 66.81; H, 5.47.

Preparation of 5-Styryl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines **31**, **32**.

(a) A mixture of 4-hydrazino-2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (3.22 g, 0.01 mole) and triethyl orthoformate or triethyl orthoacetate (20 ml) was warmed on a water bath for 30 minutes. The mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered and dried. Crystallization from a suitable solvent yielded the corresponding 5-styryl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine.

(b) A solution of 4-hydrazino-2-styryl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (3.22 g, 0.01 mole) in formic acid or acetic acid (30 ml) was refluxed for 3-4 hours. The mixture was cooled and poured into ice water. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

Isomerization of 5-Styryl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines **31**, **32** to 5-Styryl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines **22**, **23**.

A mixture of 5-styryl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine (0.01 mole) and ethanol (30 ml) containing sodium ethoxide (5-10 mg) was warmed on a water bath for 15-30 minutes and allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with ethanol and dried. Crystallization from a suitable solvent yielded the corresponding 5-styryl-1,2,4-triazolo[2,3-*c*] isomers, which were found to be identical (tlc, mp and ir) with **22**, **23** obtained by the condensation of 5-methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines with benzaldehyde.

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