Studies on the Synthesis and Interconversion of Isomeric Triazolothienopyrimidines. Part III. Cyclization Reactions of 2-Amino-3-(1*H*-1,2,4-triazol-3-yl)thiophenes

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Isolation of 2-amino-3-(1*H*-1,2,4-triazol-3-yl)thiophenes in the hydrolytic cleavage reactions of isomeric triazolothienopyrimidines is reported. The 2-amino-3-triazolylthiophenes on reaction with one carbon donors were found to cyclize to 1,2,4-triazolo[1,5-*c*]thienopyrimidines, exclusively.

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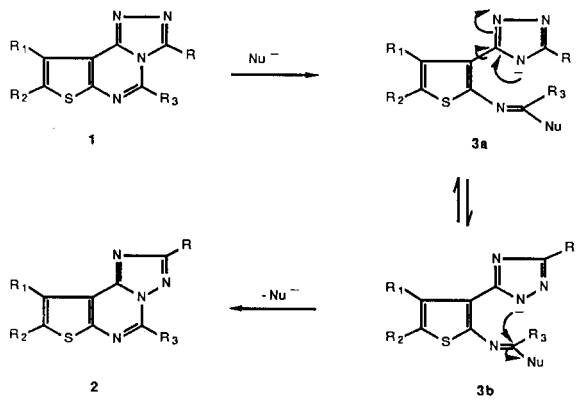
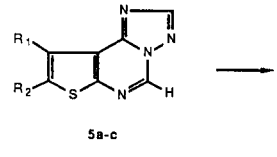
Triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines **1** have been shown to undergo isomerization to the triazolo[1,5-*c*]-thieno[3,2-*e*]pyrimidines **2** under acidic or basic conditions [1]. The envisaged mechanism presumes [1] the cleavage of N_4-C_5 bond to give a transient intermediate of the type **3a** or **3b** which then cyclizes preferentially to the thermodynamically more stable [1,5-*c*] isomer **2** rather than the [4,3-*c*] isomer **1** (Scheme I).

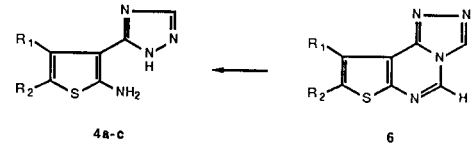
Scheme I



With the aim of isolating the ring fission intermediates of the type **3a** or **3b** and study their mode of cyclization to the isomeric triazolothienopyrimidines, the hydrolytic cleavage of triazolothienopyrimidines was undertaken.

We observed that the triazolo[1,5-*c*]thienopyrimidine **5a** on treatment with sodium hydroxide in ethanol at reflux undergoes hydrolytic cleavage to yield 2-amino-4-phenyl-3-(1*H*-1,2,4-triazol-3-yl)thiophene **4a**. The triazolylthiophene **4a** could also be obtained in 62% yield as the product of hydrolytic cleavage of 9-phenyltriazolo[4,3-*c*]-thieno[3,2-*e*]pyrimidine **6**.





4a-c 6

4a, 5a, 6, R_1 = C_6H_5, R_2 = H
4b, 5b, R_1R_2 = $-(CH_2)_4-$
4c, 5c, R_1 = R_2 = CH_3

Similarly, triazolothienopyrimidines **5b** and **5c** when treated with aqueous sodium hydroxide in refluxing ethanol yielded 2-amino-3-triazolylthiophenes **4b** and **4c**, respectively. Although, 2-amino-3-triazolylthiophenes **4b** and **4c** could not be obtained in pure form, they could, however, be carried through in the reaction sequences.

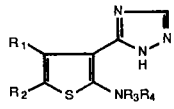
Having achieved a practical route to the otherwise inaccessible 2-amino-3-triazolylthiophenes, it was thought of interest to study their mode of cyclization with various one carbon donors such as ortho esters, acids and nitriles. These cyclizations can be expected to proceed *via* **3a** or **3b** to yield the triazolo[1,5-*c*] or [4,3-*c*]thienopyrimidines or a mixture of the two isomers [2].

The 2-amino-4-phenyl-3-triazolylthiophene **4a** on refluxing with formic acid was found to cyclize exclusively to the triazolo[1,5-*c*]thienopyrimidine **5a**. Similarly, cyclization of **4a** with acetic acid led to the formation of 5-methyltriazolo[1,5-*c*]thienopyrimidine **8** as the only isolable product. The triazolothienopyrimidines **5a** and **8** can also be obtained by the annulation of 4-hydrazinothienopyrimidines **7a** and **7b** with formic acid at reflux.

Surprisingly, 2-amino-3-triazolylthiophene **4a** when reacted with triethyl orthoformate at 40-50° yielded 9-phenyltriazolo[1,5-*c*]thienopyrimidine **5a** as the sole product. The formation of [4,3-*c*] isomer, even in traces, was, however, not observed. The possible formation of [4,3-*c*] isomer as the primary product and its subsequent isomerization to the [1,5-*c*] isomer was ruled out by the fact that triazolo[4,3-*c*]thienopyrimidines do not undergo isomerization to the [1,5-*c*] isomers even in refluxing triethyl orthoformate [1]. The aminotriazolylthiophene **4a** was also found to yield 5-methyltriazolo[1,5-*c*]thienopyrimidine **8** as the sole product on reaction with triethyl orthoacetate.

Table I

2-Amino- and 2-Substituted amino-3-(1*H*-1,2,4-triazol-3-yl)thiophenes

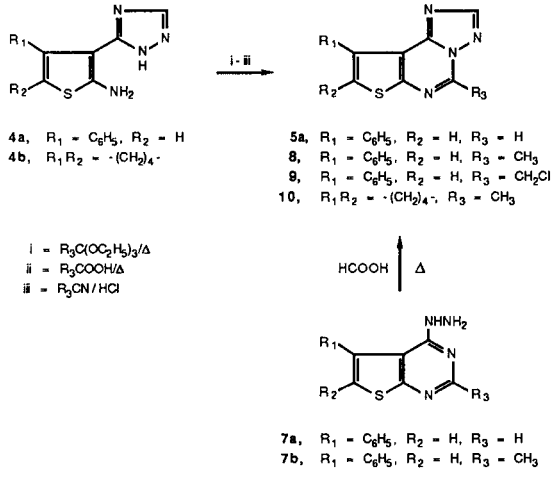


Compound No.	R_1	R_2	R_3	R_4	M.P. °C	Yield %	Recrystallization solvent [a]	Molecular formula	Molecular weight	Microanalysis Calcd/Found %C	%H
4a	C_6H_5	H	H	H	179-181	71 [c]	H-B	$C_{12}H_{10}N_4S$	242 [b]	59.48 59.16	4.16 4.48
15	-(CH$_2$)$_4$-		H	$CSNHCH_3$	211-212	61	E-C	$C_{12}H_{15}N_5S_2$	293	49.12 49.40	5.15 5.48
16	-(CH$_2$)$_4$-		H	$CSNHC_6H_{11}$	209-211	55	E-C	$C_{17}H_{23}N_5S_2$	361	56.48 56.80	6.41 6.72
17	-(CH$_2$)$_4$-		H	$CSNHC_6H_5$	268-270	51	E-C	$C_{17}H_{17}N_5S_2$	355	57.44 57.44	4.82 4.51
19	-(CH$_2$)$_4$-		$COOC_2H_5$	$COOC_2H_5$	122-124	33	E	$C_{16}H_{20}N_4SO_4$	364 [b]	52.73 53.20	5.53 5.93
20	CH_3	CH_3	$COOC_2H_5$	$COOC_2H_5$	153-155	56	E	$C_{14}H_{18}N_4SO_4$	338	49.69 49.97	5.36 5.59

[a] B = Benzene, C = Chloroform, E = Ethanol, H = *n*-Hexane. [b] Molecular weight determined by mass spectra. [c] Also obtained in 62% yield through the hydrolytic cleavage of 9-phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine.

The reaction of nitriles with *o*-aminocarbonyl compounds under acidic conditions [3] was extended to the cyclization of 2-amino-3-triazolylthiophenes. Thus, triazolylthiophenes **4a** and **4b** when reacted with chloroacetonitrile and acetonitrile in dioxane in the presence of dry hydrogen chloride gas afforded good yields of triazolo[1,5-*c*]thienopyrimidines **9** and **10**, respectively (Scheme II) (Table II).

Scheme II



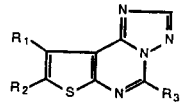
These results indicate that the intermediates of the type **3a** or **3b** cyclize exclusively to the thermodynamically more stable triazolo[1,5-*c*] isomers. The observed preferential cyclization of **3a** or **3b** to the [1,5-*c*] isomers through the nucleophilic attack by the vicinal nitrogen (N_2) rather than by the N_4 nitrogen parallels the observation of preferential alkylations and acylations at the vicinal nitrogen atoms in the 1,2,4-triazoles [4].

The 2-amino-3-triazolylthiophenes **4b** and **4c** were also utilized for the synthesis of some triazolo[1,5-*c*]thienopyrimidines with a functional substituent at the 5-position which are, otherwise, not readily accessible.

Thus, the reaction of **4b** and **4c** with carbon disulphide in the presence of potassium hydroxide in ethanol yielded 5-mercapto-1,2,4-triazolo[1,5-*c*]thienopyrimidines **11** and **12**, respectively. Methylation of **11** and **12** with dimethyl sulphate in ethanolic potassium hydroxide was found to yield the corresponding 5-methylthio-derivatives **13** and **14** (Scheme III). Alkyl and aryl isothiocyanates react with **4b** in ethanol to yield the thioureas **15-17**. Attempted cyclization of the thiourea **17** in the presence of concentrated hydrochloric acid was found to proceed with the elimination of aniline to yield the 5-mercaptotriazolothienopyrimidine **11**. However, the thiourea **16** was found to cyclize to the 5-cyclohexylaminotriazolo[1,5-*c*]thienopyrimidine **18** on methylation with methyl iodide in the presence of potassium carbonate in dioxane. The cycliza-

Table II

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

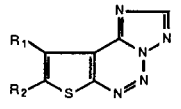


Compound No.	R_1	R_2	R_3	M.P. °C	Yield %	Recrystallization solvent [a]	Molecular formula	Molecular weight	Microanalysis Calcd/Found %C	%H
5a	C_6H_5	H	H	196-198	65 [c]	E-C	$C_{13}H_8N_4S$	252 [b]	61.88	3.20
									61.96	3.37
5c	CH_3	CH_3	H	194-196	60 [d]	E	$C_9H_8N_4S$	204	52.92	3.95
									53.29	4.26
8	C_6H_5	H	CH_3	145-146 [e]	45 [f]	M-C	$C_{14}H_{10}N_4S$	266		
9	C_6H_5	H	CH_2Cl	184-185	66	H-B	$C_{14}H_9N_4SCl$	300.5	55.90	3.02
									55.91	3.33
10	-$(CH_2)_4$-		CH_3	156-157 [g]	45	M-C	$C_{12}H_{12}N_4S$	244		
11	-$(CH_2)_4$-		SH	257-259	65 [h]	E-C	$C_{11}H_{10}N_4S_2.H_2O$	262 [b]	47.12	4.31
									46.73	4.70
12	CH_3	CH_3	SH	259-261	51	E-C	$C_9H_8N_4S_2$	236	45.74	3.41
									46.07	3.64
13	-$(CH_2)_4$-		SCH_3	170-172	58	E	$C_{12}H_{12}N_4S_2$	276	52.15	4.38
									52.42	4.70
14	CH_3	CH_3	SCH_3	199-201	72	E	$C_{10}H_{10}N_4S_2$	250 [b]	47.97	4.03
									48.35	4.32
18	-$(CH_2)_4$-		NHC_6H_{11}	188-190	43	H	$C_{17}H_{21}N_5S$	327 [b]	62.35	6.47
									62.25	6.73

[a] B = Benzene, C = Chloroform, D = Dimethylformamide, E = Ethanol, H = *n*-Hexane, M = Methanol. [b] Molecular weight determined by mass spectra. [c] Also obtained in 83% yield through the reaction of 4-hydrazino-5-phenylthieno[2,3-*d*]pyrimidine with formic acid at reflux and in 48% yield through the reaction of **4a** with triethyl orthoformate. [d] Obtained through the cyclization of 5,6-dimethyl-4-hydrazinothieno[2,3-*d*]pyrimidine with formic acid at reflux. [e] Reported mp 145-146° [1]. [f] Also obtained in 68% yield through the cyclization of **4a** with triethyl orthoacetate. [g] Reported mp 156-157° [1]. [h] Also obtained in 57% yield through the cyclization of **17** in concentrated hydrochloric acid.

Table III

1,2,4-Triazolo[1,5-*c*]thieno[3,2-*e*]-1,2,3-triazines



Compound No.	R_1	R_2	M.P. °C	Yield %	Recrystallization solvent [a]	Molecular formula	Molecular weight	Microanalysis Calcd/Found %C	%H
21	-$(CH_2)_4$-		203-204	43	E-C	$C_{10}H_9N_5S$	231	51.93	3.92
								51.67	4.22
22	CH_3	CH_3	177-179	63	E	$C_8H_7N_5S$	205	46.81	3.44
								46.89	3.69

[a] C = Chloroform, E = Ethanol.

tion, probably, proceeds through *S*-methylation, followed by the elimination of methyl mercaptan.

The reaction of aminotriazolylthiophenes **4b** and **4c** with ethyl chloroformate in benzene yielded the dicarb-

Table IV

Spectral Data of 2-Amino-3-triazolylthiophenes, Triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines and Triazolo[1,5-*c*]thieno[3,2-*e*]-1,2,3-triazines

Compound No.	IR (cm^{-1}) [a]	^{1}H-NMR (δ ppm) [b]	MS: m/e
4a	3360, 3240, 3120 (NH) [A]	6.3 (2H, s, NH_2), 7.33 (1H, s, NH), 7.5 (6H, m, Ar-H and H at C_5), 7.93 (1H, s, H at C_5 of triazole)	242 (M^+), 241, 226, 214, 209, 200, 198, 187, 186, 182, 155, 140.
5a	1605 [A]	–	–
5c	1610 [B]	–	–
9	1610 [A]	–	–
11	1615 [B]	–	262 (M^+), 261, 247, 235, 234, 233, 229, 221, 207, 206, 188, 176, 175, 174, 162, 161, 160, 149.
12	1600 [A]	–	–
13	1610 [B]	2.0 (4H, m, CH_2 at C_9 and C_{10}), 3.0 (7H, m, CH_2 at C_8 and C_{11} and S-CH_3), 8.38 (1H, s, CH at C_2)	–
14	1610 [A]	–	250 (M^+), 249, 235, 221, 218, 208, 203, 189, 177, 176, 162, 150, 149, 135, 122.
15	3300, 3140 (NH) [B]	–	–
16	3280 (NH) [B]	–	–
17	3400, 3260, 3180-3120 (NH) [A]	–	–
18	3400, 3390, 3380 (NH) [B]	–	327 (M^+), 326, 300, 299, 298, 284, 272, 271, 270, 258, 244, 230, 217, 216, 202, 190, 189, 175, 160.
19	3220 (NH), 1795, 1715 (C=O) [A]	–	364 (M^+), 336, 319, 292, 291, 274, 264, 259, 246, 232, 231, 218, 204, 203, 191, 176, 175, 163, 148.
20	3200 (NH), 1800, 1710 (C=O) [B]	–	–
21	1600 [B]	–	–
22	1600 [B]	2.8 (3H, s, CH_3), 2.9 (3H, s, CH_3), 8.5 (1H, s, H at C_2)	–

[a] Measured in: A = Potassium bromide, B = Nujol. [b] Measured solvent: Deuteriochloroform.

ethoxyamino-derivatives **19** and **20**, respectively [5] (Table I).

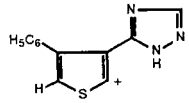
The diazotization of 2-amino-3-triazolylthiophenes **4b** and **4c** with nitrous acid in acetic acid at 0-5° yields the aza-analogues of thienopyrimidine, the 1,2,4-triazolo-[1,5-*c*]thieno[3,2-*e*]-1,2,3-triazines **21** and **22**, respectively (Table III).

Thus, 2-amino-3-(1*H*-1,2,4-triazol-3-yl)thiophenes obtained by the ring cleavage of triazolothienopyrimidines could be employed as excellent starting materials for the synthesis of a variety of 5-substituted triazolo[1,5-*c*]thieno-pyrimidines.

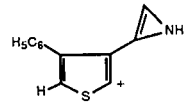
The spectrum of 2-substituted amino-3-triazolylthiophenes **15-17, 19** and **20** exhibits the N-H stretching absorption in the region 3400-3120 cm^{-1}. The C=O stretching absorption of the compounds **19** and **20** appears around 1800-1715 cm^{-1}. While the ir spectrum of triazolothienopyrimidines **5a, 8-14** are devoid of any absorption in the region 3400-3280 cm^{-1}, the 5-substituted aminotriazolothienopyrimidine **18** exhibits N-H stretching absorptions at 3400-3380 cm^{-1} (Table IV).

The triazole proton singlet (N-C_2) in the ^{1}H-nmr spectrum of triazolothienopyrimidine **13** appears at an upfield value of δ 8.3 lending support to the structural assignments made for these compounds. Similarly, the proton singlet in the triazolothienotriazine **22** was found to occur at δ 8.5, thus confirming its structural assignment.

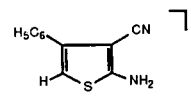
The mass spectrum of 2-amino-3-triazolylthiophene **4a** exhibits an intense parent ion peak at m/e 242. The successive loss of NH_2 and N_2 from the molecular ion gives ions **23** and **24**. The intense peak at m/e 200 is assignable to the radical cation **25** arising by the loss of HN–CH from the molecular ion.



23, m/e 226



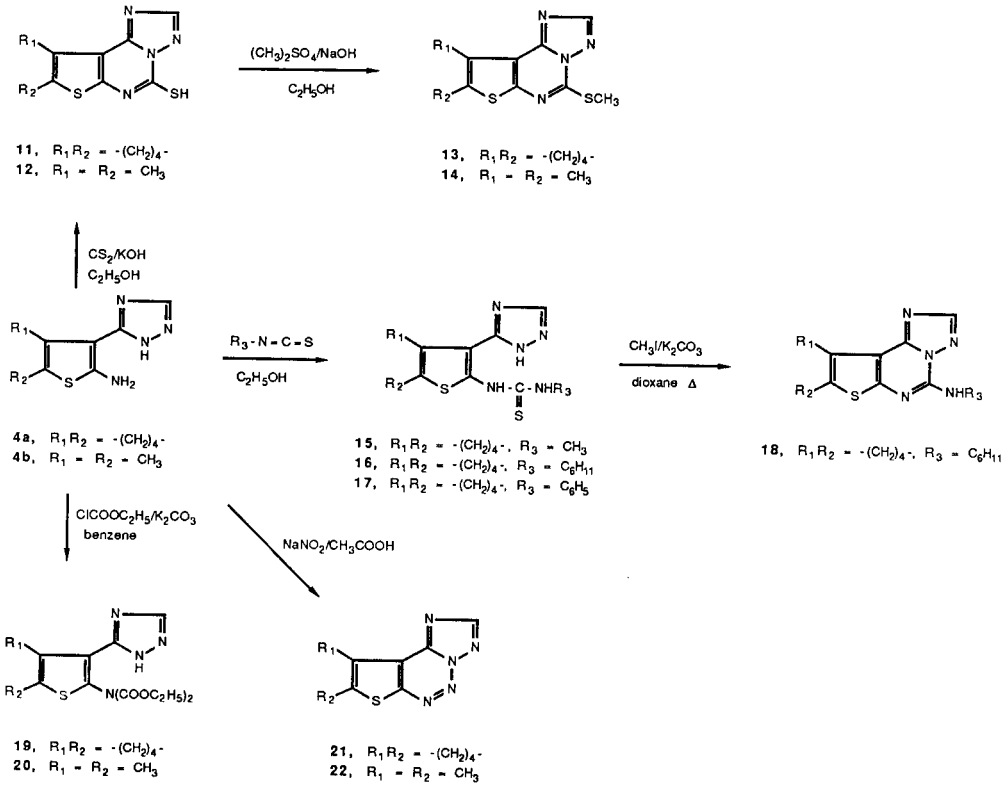
24, m/e 198



25, m/e 200

The spectrum of 5-substituted triazolothienopyrimidines **11, 14** and **18** exhibits intense molecular ion peaks. Elimination of N_2 from the triazole ring appears to be an important mode of fragmentation of these compounds.

Scheme III



11, R_1R_2 = -$(CH_2)_4$-
12, R_1 = R_2 = CH_3

13, R_1R_2 = -$(CH_2)_4$-
14, R_1 = R_2 = CH_3

4a, R_1R_2 = -$(CH_2)_4$-
4b, R_1 = R_2 = CH_3

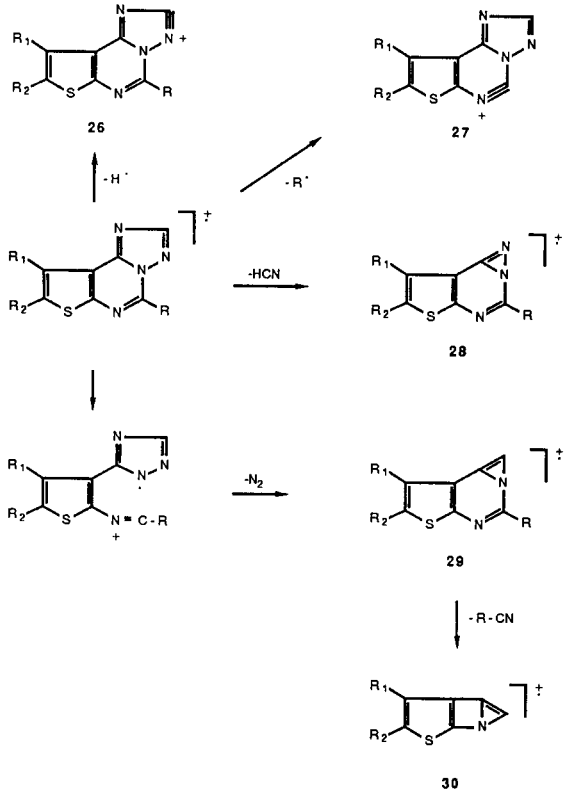
15, R_1R_2 = -$(CH_2)_4$-, R_3 = CH_3
16, R_1R_2 = -$(CH_2)_4$-, R_3 = C_6H_{11}
17, R_1R_2 = -$(CH_2)_4$-, R_3 = C_6H_5

18, R_1R_2 = -$(CH_2)_4$-, R_3 = C_6H_{11}

19, R_1R_2 = -$(CH_2)_4$-
20, R_1 = R_2 = CH_3

21, R_1R_2 = -$(CH_2)_4$-
22, R_1 = R_2 = CH_3

Scheme IV



26

27

28

29

30

The loss of R-CN from the radical cation **29** accounts for the formation of ion **30**. Some of the significant peaks in the spectra of triazolothienopyrimidines are probably due to the ions **26, 27** and **28** arising by the loss of H·, R· and HCN from the molecular ion (Scheme IV).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded in nujol mulls or potassium bromide on a Perkin Elmer 337 Grating spectrophotometer. The ^{1}H-nmr spectra were taken on a Varian A-60 spectrometer using TMS as the internal standard. The mass spectra were obtained on a Varian Atlas CH-7 spectrometer at 70 ev ionizing beam, using direct insertion probe. The starting material **5b** was prepared by literature method [1].

Preparation of 9-Phenyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine **5a**.

A solution of 4-hydrazino-5-phenylthieno[2,3-*d*]pyrimidine (2.42 g, 0.01 mole) in formic acid (25 ml) was refluxed for 4 hours. The solvent was removed under vacuum and the residue was triturated with water. The solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform yielded colorless crystals of **5a**, mp 196-198°, yield 1.6 g (83%).

Similarly, 8,9-dimethyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine **5c** was obtained by the cyclization of 4-hydrazino-5,6-dimethylthieno-[2,3-*d*]pyrimidine with refluxing formic acid.

Preparation of 9-Phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine **6**.

A mixture of 4-hydrazino-5-phenylthieno[2,3-*d*]pyrimidine (2.42 g, 0.01 mole) and triethyl orthoformate (20 ml) was refluxed for 5 hours. The reaction mixture was cooled, the solid obtained was filtered and dried. Crystallization from ethanol-chloroform afforded 2.2 g (88%) of **6**, mp 239-241°; ir: (cm^{-1}) 1600.

Anal. Calcd. for $C_{13}H_8N_4S$: C, 61.88; H, 4.18. Found: C, 62.15; H, 3.45.

Preparation of 2-Amino-4-phenyl-3-(1*H*-1,2,4-triazol-3-yl)thiophene **4a**.

To a stirred suspension of 9-phenyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]-pyrimidine **5a** (2.52 g, 0.01 mole) in ethanol (25 ml) was added a solution of sodium hydroxide (15 ml, 2 *N*). The reaction mixture was refluxed for 2 hours, cooled and poured into ice-water (125 ml). The solution was clarified by filtration and the clear filtrate was acidified with 10% acetic acid. The solid obtained was filtered, washed with water and dried. Crystallization from *n*-hexane-benzene gave 1.8 g (71%) of **4a**, mp 179-181°.

2-Amino-4-phenyl-3-triazolylthiophene **4a** was also obtained in 62% by the hydrolysis of 9-phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine **6** with ethanolic sodium hydroxide solution according to the procedure described above.

Similarly, 2-amino-3-triazolylthiophenes **4b** and **4c** were obtained by the hydrolytic cleavage of the corresponding 1,2,4-triazolo[1,5-*c*]-thieno[3,2-*e*]pyrimidines according to the method described above for the preparation of **4a** and were used in reactions without purification.

Cyclization Reactions of 2-Amino-3-triazolylthiophenes.

Preparation of 9-Phenyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine **5a**.

a) A solution of 2-amino-4-phenyl-3-triazolylthiophene **4a** (2.42 g, 0.01 mole) in formic acid (20 ml) was refluxed for 2 hours. The reaction mixture was cooled and poured into ice-water. The solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform afforded 1.6 g (65%) of **5a** as colorless crystals, mp 196-198°, identical (mmp, tlc, ir) with the product obtained by the cyclization of 4-hydrazino-5-phenylthieno[2,3-*d*]pyrimidine with formic acid at reflux.

b) A suspension of **4a** (2.42 g, 0.01 mole) in triethyl orthoformate (15 ml) was heated on a water bath at 50-60° for 10-15 minutes and cooled. The solid obtained was filtered and dried. Crystallization from ethanol-chloroform gave 1.2 g (48%) of **5a**.

Preparation of 5-Methyl-9-phenyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine **8**.

a) A suspension of **4a** (2.42 g, 0.01 mole) in acetic acid (25 ml) was refluxed for 5-10 minutes and allowed to stand at room temperature for 12 hours. The reaction mixture was poured into ice-water and the solid obtained was filtered, washed with water and dried. Crystallization from methanol-chloroform gave 1.2 g (45%) of **8**, mp 145-146°, identical (mmp, tlc, ir) with the product obtained by the cyclization of 2-methyl-4-hydrazino-5-phenylthieno[2,3-*d*]pyrimidine with formic acid at reflux [1].

b) A suspension of **4a** (2.42 g, 0.01 mole) in triethyl orthoacetate (25 ml) was heated on a water bath at 50-60° for 10-15 minutes and cooled. The solid obtained was filtered and dried. Crystallization from methanol-chloroform yielded 1.0 g (68%) of **8**, mp 145-146°.

Preparation of 5-Chloromethyl-9-phenyl-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]-pyrimidine **9**.

A stream of dry hydrogen chloride gas was passed through a solution of **4a** (2.42 g, 0.01 mole) and chloroacetonitrile (0.91 g, 0.012 mole) in dioxane (30 ml) for 5 hours with external cooling in an ice bath. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Crystallization from *n*-hexane-benzene afforded 2.0 g (66%) of **9**, mp 184-185°.

Preparation of 5-Methyl-1,2,4-triazolo[1,5-*c*]-8,9,10,11-tetrahydrobenzo-[*b*]thieno[3,2-*e*]pyrimidine **10**.

A stream of dry hydrogen chloride gas was passed through a solution of **4b** (2.2 g, 0.01 mole) in excess of acetonitrile (25 ml) for 5 hours with external cooling in an ice bath. The mixture was poured into ice-water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water and dried. Crystallization from methanol-chloroform afforded 1.1 g (45%) of colorless crystals of **10**, mp 156-157°, identical (mmp, tlc, ir) with the product obtained by the cyclization of 2-methyl-4-hydrazino-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidine with formic acid at reflux [1].

General Procedure for the Preparation of 5-Mercapto-1,2,4-triazolo-[1,5-*c*]thieno[3,2-*e*]pyrimidines **11** and **12**.

To a solution of an appropriate 2-amino-3-triazolylthiophene (0.01 mole) and potassium hydroxide (85%) (0.66 g, 0.01 mole) in absolute ethanol (50 ml) was added, with stirring, carbon disulphide (1.5 g, 0.02 mole). The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and acidified with dilute acetic acid. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

General Procedure for the Preparation of 5-Methylthio-1,2,4-triazolo-[1,5-*c*]thieno[3,2-*e*]pyrimidines **13** and **14**.

To a solution of 5-mercapto-1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine (0.01 mole) and potassium hydroxide (85%) (0.66 g, 0.01 mole) in absolute ethanol (50 ml) was added dropwise dimethyl sulphate (1.26 g, 0.01 mole). The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

General Procedure for the Preparation of N^2-Substituted-N^1-[3-(1,2,4-triazol-3-yl)thien-2-yl]thioureas **15-17**.

To a suspension of 2-amino-3-(1*H*-1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (2.2 g, 0.01 mole) in ethanol (25 ml) was added an appropriate isothiocyanate (0.01 mole). The reaction mixture was refluxed for 2 hours and cooled. The solid obtained was filtered, washed with cold ethanol, dried and crystallized from a suitable solvent.

Preparation of 5-Cyclohexylamino-1,2,4-triazolo[1,5-*c*]-8,9,10,11-tetrahydrobenzo[*b*]thieno[3,2-*e*]pyrimidine **18**.

A mixture of N^2-cyclohexyl-N^1-[3-(1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl]thiourea **16** (3.6 g, 0.01 mole) and anhydrous potassium carbonate (1.38 g, 0.01 mole) in dioxane (25 ml) was cooled to 10-15° and treated dropwise with methyl iodide (2.0 g, 0.02 mole). The reaction mixture was allowed to stand at room temperature for 12 hours and heated on a water bath until evolution of methyl mercaptan ceased. The reaction mixture was poured into ice-water, the solid obtained was filtered, washed successively with water, 10% sodium hydroxide solution and water. Crystallization from *n*-hexane yielded 1.4 g (43%) of **18**, mp 188-190°.

Cyclization of N^2-Phenyl-N^1-[3-(1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo-[*b*]thien-2-yl]thiourea **17** in the Presence of Hydrochloric Acid.

A suspension of **17** (3.55 g, 0.01 mole) in concentrated hydrochloric acid (30 ml) was refluxed for 10-15 minutes. The reaction mixture was cooled and poured into ice-water. The solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform yielded 1.5 g (57%) of **11**, mp 257-259°, identical (mmp, tlc, ir) with the product obtained by the reaction of 2-amino-3-(1*H*-1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene **5b** with carbon disulphide.

General Procedure for the Preparation of 2-(*N,N*-Dicarbethoxyamino)-3-(1*H*-1,2,4-triazol-3-yl)thiophenes **19** and **20**.

To a mixture of an appropriate 2-amino-3-triazolylthiophene (0.01 mole) and anhydrous potassium carbonate (2.07 g, 0.015 mole) in benzene (50 ml) was added dropwise, with stirring, ethyl chloroformate (1.3 g, 0.012 mole). The reaction mixture was refluxed for 5 hours and filtered hot. The filtrate was washed with water, dried and concentrated. The semisolid residue was triturated with ethanol. The solid obtained was filtered, washed with cold ethanol, dried and crystallized from a suitable solvent.

General Procedure for the Preparation of 1,2,4-Triazolo[1,5-*c*]thieno-[3,2-*e*]-1,2,3-triazines **21** and **22**.

A solution of an appropriate 2-amino-3-triazolylthiophene (0.01 mole)

in acetic acid (50 ml, 50% w/v) was cooled to 0-5° in an ice bath and treated dropwise with a solution of sodium nitrite (1.03 g, 0.015 mole) in water (10 ml). The reaction mixture was stirred at 0-5° for 30 minutes and the solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

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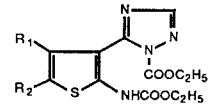
[5] Alternate formulation as 2-(*N*-carbethoxyamino)-3-(1-carbethoxy-1,2,4-triazol-3-yl)thiophene **31** to these derivatives cannot be ruled out.



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