Studies in the Synthesis and Interconversion of Isomeric Triazolothienopyrimidines

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4-Hydrazinothieno[2,3-*d*]pyrimidines were cyclized with triethyl orthoformate and formic acid to give 1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines and 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines depending on the reaction conditions employed.

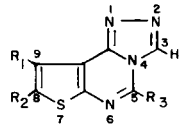
J. Heterocyclic Chem., **18**, 43 (1981).

Condensed triazoles possess a variety of pharmacological activities like mitotic (1), hypotensive (2), CNS stimulant (3), antiinflammatory (4,5) and analgesic activity (6,7). In continuation of our earlier work on thienopyrimidines (8), we were interested in the synthesis of triazolothienopyrimidines as potential antiinflammatory compounds.

The synthesis of 1,2,4-triazolothieno[2,3-*d*]pyrimidine system has been reported by a number of workers (9-12). In many instances, formic acid has been used for the cyclization of 4-hydrazinothieno[2,3-*d*]pyrimidines to the corresponding triazoles. The products obtained in all these cases were assigned the 1,2,4-triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidine structure (9,10). The possibility of the formation of isomeric triazoles in the cyclization of the hydrazines with different cyclizing agents appears to have been overlooked by these workers. It was, therefore, thought of interest to study the cyclization of 4-hydrazinothieno[2,3-*d*]pyrimidines with formic acid as well as triethyl orthoformate under different reaction conditions and study the nature of the products formed.

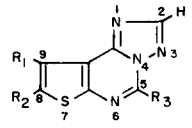
Results and Discussions.

The 4-hydrazinothieno[2,3-*d*]pyrimidines (13) when refluxed with triethyl orthoformate (method A) gave a series of triazoles **1a-1f**. On the other hand, refluxing with formic acid (method B) afforded another series of triazoles **2a-2j**. The two isomeric series of triazoles showed no appreciable difference in the fragmentation pattern under electron impact. However, the nmr spectra showed considerable difference in the absorption of triazole protons. While the compounds **1a-1f** exhibit the triazole proton absorption around δ 9.3, the triazole proton of the compounds **2a-2f** appears to be more shielded and exhibits a singlet at δ 8.3. The compounds **1a-1f** obtained by the cyclization with triethyl orthoformate, exhibiting much deshielded signal are assigned the 1,2,4-triazolo[4,3-*c*]-thieno[3,2-*e*]pyrimidine structure **1**, while the triazoles **2a-2j** obtained by the cyclization with formic acid at reflux are assigned the 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]-pyrimidine structure **2**. Similar assignments have been reported in the quinazoline series (14).



1

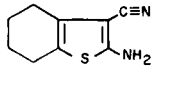
(a) R_1R_2 = -$(CH_2)_4$-, R_3 = CH_3
(b) R_1R_2 = -$(CH_2)_4$-, R_3 = H
(c) R_1R_2 = -$(CH_2)_4$-, R_3 = $CH_2C_6H_5$
(d) R_1 = R_2 = R_3 = CH_3
(e) R_1 = R_2 = CH_3, R_3 = $CH_2C_6H_5$
(f) R_1 = C_6H_5, R_2 = H, R_3 = CH_3



2

(a) R_1R_2 = -$(CH_2)_4$-, R_3 = CH_3
(b) R_1R_2 = -$(CH_2)_4$-, R_3 = H
(c) R_1R_2 = -$(CH_2)_4$-, R_3 = $CH_2C_6H_5$
(d) R_1 = R_2 = R_3 = CH_3
(e) R_1 = R_2 = CH_3, R_3 = $CH_2C_6H_5$
(f) R_1 = C_6H_5, R_2 = H, R_3 = CH_3
(g) R_1 = C_6H_5, R_2 = H, R_3 = $CH_2C_6H_5$
(h) R_1R_2 = $(CH_2)_4$-, R_3 = C_6H_5
(i) R_1 = R_2 = CH_3, R_3 = C_6H_5
(j) R_1 = C_6H_5, R_2 = H, R_3 = C_6H_5

In order to achieve an unambiguous synthesis of one of the isomeric triazoles, the orthoaminonitrile **3** (15) was condensed with triethyl orthoacetate. The intermediate *N*-substituted acetiminoether **4** was reacted with hydrazine hydrate. The product was 3-amino-4-imino-2-methyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine **5** as indicated by its physical and spectral characteristics which are different from that of the 4-hydrazinothieno-[2,3-*d*]pyrimidine **6**. The compound **5** on reaction with triethyl orthoformate gave a product which is identical in all respects with that of **2a** obtained from the reaction of 4-hydrazino-2-methylthieno[2,3-*d*]pyrimidine **6** with formic acid at reflux, thus lending additional support to the structural assignments made.



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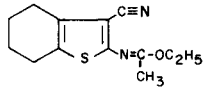

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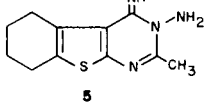

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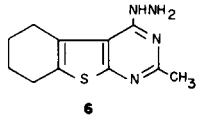

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It appears that when formic acid at reflux is used for the cyclization, the initial product formed is the [4,3-*c*]-triazole which then undergoes rearrangement to the [2,3-*c*]

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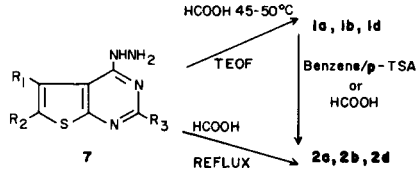
isomer. This fact is borne out of our observation that the compound **1a** is indeed the only isolable product of the reaction when the 4-hydrazino compound **6** was reacted with formic acid at 45-50° (method C) instead of at reflux temperature. Likewise, reacting 4-hydrazinothieno[2,3-*d*]-pyrimidine **7** with formic acid at 45-50° resulted in the [4,3-*c*]triazoles **1b** and **1d**.



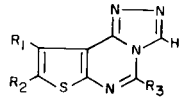
The [4,3-*c*] isomer could also be rearranged to the [2,3-*c*] isomer by refluxing the former in benzene in the presence of *p*-toluenesulfonic acid or by refluxing in formic acid. The course of the rearrangement was followed by tlc of the reaction mixture at different time intervals. The rearrangement sets in about 15 minutes and is complete after about 3 hours. Thus, compounds **1a, 1d** and **1f** could be rearranged to **2a, 2d** and **2f**, respectively.

It is interesting to note that the compounds of Table I **1a-1f** show the longer wavelength absorption in uv at around 305 nm and those of Table II **2a-2f** at around 295 nm. Further, the compounds of Table I have higher melting points than those belonging to Table II.

When 4-hydrazino-2-phenylthieno[2,3-*d*]pyrimidines **8** were cyclized either with triethyl orthoformate or formic acid at reflux, the triazolo[2,3-*c*]theino[3,2-*e*]pyrimidines were the only products isolable **2h-2j**. The isolation of the same isomer irrespective of the conditions employed for the cyclization and the fact that the triazoles obtained could not be isomerised under acidic conditions indicates

Table I

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

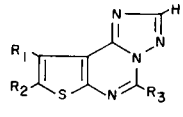


Compound No.	R_1	R_2	R_3	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	Microanalysis %C Calcd.	%C Found	%H Calcd.	%H Found	Uv λ max (log ε)	Nmr δ H_3 (b)	Solvent (c)
1a	-$(CH_2)_4$-		CH_3	272-274	71	M-C	$C_{12}H_{12}N_4S$	244	59.02	58.95	4.92	4.87	228 (4.50), 252 (4.50), 308 (4.36)	9.5 (s) 9.4 (s)	CT T
1b	-$(CH_2)_4$-		H	306-308	87	M-C	$C_{11}H_{10}N_4S$	230	57.39	57.75	4.38	4.73	222 (4.58), 250 (4.36), 308 (4.14)	9.4 (s) 9.6 (s)	CT T
1c	-$(CH_2)_4$-		$CH_2C_6H_5$	222-223	71	E-C	$C_{18}H_{16}N_4S$	320	67.48	67.73	5.03	5.34	226 (4.51), 252 (4.47), 310 (4.40)	9.2 (s)	T
1d	CH_3	CH_3	CH_3	228-230	69	E-C	$C_{10}H_{10}N_4S$	218	55.04	55.18	4.62	4.92	226 (4.54), 251 (4.50), 305 (4.32)	9.3 (s) 9.54 (s) 9.4 (s)	CT D T
1e	CH_3	CH_3	$CH_2C_6H_5$	201-204	69	M-C	$C_{16}H_{14}N_4S$	294	65.30	65.62	4.80	4.54	226 (4.54), 252 (4.48), 309 (4.39)	9.3 (s)	CT
1f	C_6H_5	H	CH_3	249-255	55	M-C	$C_{14}H_{10}N_4S$	266	63.15	63.19	3.79	3.99	224 (4.52), 252 (4.49), 308 (4.38)	9.5 (s) 9.4 (s)	D T

(a) E = ethanol, M = methanol, C = chloroform. (b) Chemical shifts are given in ppm relative to tetramethylsilane as internal standard. Line shape: s = singlet. (c) CT = deuteriochloroform + trifluoracetic acid, C = deuteriochloroform, D = DMSO-d_6, T = trifluoroacetic acid.

Table II

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

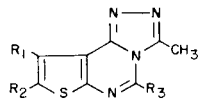


Compound No.	R_1	R_2	R_3	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	Microanalysis %C Calcd.	%C Found	%H Calcd.	%H Found	Uv λ max (log ε)	Nmr δ H_2 (b)	Solvent (c)
2a	-$(CH_2)_4$-		CH_3	156-157	66	M-C	$C_{12}H_{12}N_4S$	244	59.02	59.44	4.92	5.18	248 (4.67), 292 (4.38)	8.2 (s)	C
2b	-$(CH_2)_4$-		H	138-139	65	M	$C_{11}H_{10}N_4S$	230	57.39	57.71	4.38	4.53	248 (4.44), 295 (4.38)	8.3 (s)	C
2c	-$(CH_2)_4$-		$CH_2C_6H_5$	140-143	81	M-C	$C_{18}H_{16}N_4S$	320	67.48	67.26	5.03	5.30	247 (4.65), 297 (4.41)	8.3 (s)	C
2d	CH_3	CH_3	CH_3	163-165	83	M-C	$C_{10}H_{10}N_4S$	218	55.04	55.19	4.62	4.92	246 (4.64), 290 (4.34)	8.2 (s)	C
2e	CH_3	CH_3	$CH_2C_6H_5$	152-154	62	M-C	$C_{16}H_{14}N_4S$	294	65.30	65.32	4.80	5.11	248 (4.68), 294 (4.45)	8.2 (s)	C
2f	C_6H_5	H	CH_3	145-146	60	M-C	$C_{14}H_{10}N_4S$	266	63.15	63.10	3.79	4.00	248 (4.62), 295 (4.32)	8.25 (s)	C
2g	C_6H_5	H	$CH_2C_6H_5$	133-136	66	M-C	$C_{20}H_{14}N_4S$	342	70.16	70.39	4.12	4.36	248 (4.69), 291 (4.26)	8.30 (s)	C
2h	-$(CH_2)_4$-		C_6H_5	207-210	60	M-C	$C_{17}H_{14}N_4S$	306	66.65	66.45	4.57	4.85	232 (4.57), 335 (4.44)	8.9 (s)	C
2i	CH_3	CH_3	C_6H_5	229-231	90	M-C	$C_{15}H_{12}N_4S$	280	64.27	64.06	4.32	4.72	230 (4.57), 335 (4.45)	8.9 (s)	C
2j	C_6H_5	H	C_6H_5	233-235	63	M-C	$C_{19}H_{12}N_4S$	328	69.50	69.71	3.65	4.00	230 (4.63), 332 (4.47)	8.9 (s)	C

(a) M = methanol, C = chloroform. (b) Chemical shifts are given in ppm relative to tetramethyl silane as internal standard. Line shapes: s = singlet. (c) C = deuteriochloroform.

Table III

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

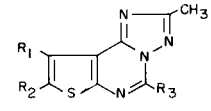


Compound No.	R_1	R_2	R_3	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	Micro Analysis %C Calcd.	%C Found	%H Calcd.	%H Found	Uv λ max (log ε)
9a	-(CH$_2$)$_4$-		CH$_3$	273-275	73	M-C	$C_{13}H_{14}N_4S$	258	60.45	60.12	5.46	5.69	229 (4.25), 254 (4.54), 310 (4.28)
9b	CH$_3$	CH$_3$	CH$_3$	290-292	78	M-C	$C_{11}H_{12}N_4S$	232	56.89	56.64	5.17	5.42	230 (4.66), 254 (4.33), 306 (4.05)
9c	C$_6$H$_5$	H	CH$_3$	224-226	75	M-C	$C_{15}H_{12}N_4S$	280	64.28	64.21	4.28	4.54	228 (4.51), 252 (4.50), 308 (4.32)

(a) M = methanol, C = chloroform.

Table IV

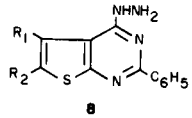
2-Methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines



Compound No.	R_1	R_2	R_3	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	Micro Analysis %C Calcd.	%C Found	%H Calcd.	%H Found	Uv λ max (log ε)
10a	-(CH$_2$)$_4$-		CH$_3$	181-183	70	E	$C_{13}H_{14}N_4S$	258	60.45	60.80	5.46	5.83	248 (4.41), 291 (4.35)
10b	CH$_3$	CH$_3$	CH$_3$	159-161	52	M-C	$C_{11}H_{12}N_4S$	232	56.89	56.86	5.17	5.45	250 (4.34), 292 (3.94)
10c	C$_6$H$_5$	H	CH$_3$	178-179	63	M-C	$C_{15}H_{12}N_4S$	280	64.28	64.43	4.28	4.63	248 (4.64), 294 (4.38)

(a) E = ethanol, M = methanol, C = chloroform.

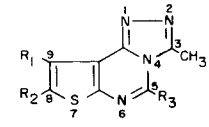
that the isomer obtained in these cases is more stable triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine **2**.



8

Our structural assignment for the isomeric triazolothienopyrimidines is in accordance with that of Sauter and Stanetty (11), but at variance with that of other workers (9,10).

When 4-hydrazinothieno[2,3-*d*]pyrimidines were cyclized with triethyl orthoacetate (method D) and acetic acid (method E), again two series of triazoles were obtainable **9a-9c** and **10a-10c**. The uv spectra of the compounds **9a-9c** obtained with triethyl orthoacetate resemble remarkably that of the [4,3-*c*] isomers obtained with triethyl orthoformate, while the uv spectra of acetic acid cyclization products **10a-10c** resembled that of the [2,3-*c*] isomers. It has also been found that the compound **9b** can be rearranged to **10b** under acidic conditions. Therefore, compounds **9a-9c** are assigned the 3-methyl-1,2,4-triazolo-[4,3-*c*]thieno[3,2-*e*]pyrimidine structure, while the triazoles **10a-10c** are assigned the 2-methyl 1,2,4-triazolo[2,3-*c*]-thieno[3,2-*e*]pyrimidine structure.



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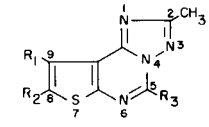


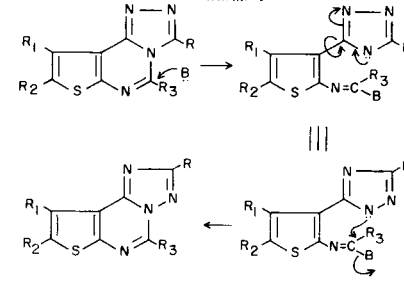
10

(a) R_1R_2 = -(CH$_2$)$_4$-, R_3=CH$_3$
(b) R_1=R_2=R_3=CH$_3$
(c) R_1=C$_6$H$_5$, R_2=H, R_3=CH$_3$

(a) R_1R_2 = -(CH$_2$)$_4$- R_3=CH$_3$
(b) R_1=R_2=CH$_3$
(c) R_1=C$_6$H$_5$, R_2=H, R_3=CH$_3$

It appears that the triazole formation from hydrazino azine in the presence of a cyclizing agent, proceeds through the initial formation of triazolo[4,3-*c*] derivative which under suitable conditions undergoes rearrangement to the stable triazolo[2,3-*c*] derivative. The isomerization of triazole seems to proceed through a sequence of ring opening and ring closure reactions (Scheme I). The difference in the stability (14) between the two isomeric triazoles seems to be another factor responsible for the formation and isomerization of the triazoles.

Scheme I



EXPERIMENTAL

All melting points are uncorrected. Ultra-violet absorption spectra were determined in 95% ethanol using Beckman Model 25 spectrophotometer. Infrared spectra were taken in nujol mulls. Nmr spectra were run on a Varian A60 spectrophotometer. Mass spectra was recorded on a Varian-Atlas CH-7 mass spectrophotometer at 70 eV ionising beam and using direct insertion probe.

Method A. General Procedure for the Preparation of 1,2,4-Triazolo-[4,3-*c*]thieno[3,2-*e*]pyrimidines (**1a-1f**).

A mixture of 4-hydrazinothieno[2,3-*d*]pyrimidines (0.02 mole) and excess of triethyl orthoformate (25 ml.) was refluxed on an oil bath for 6 hours. Excess of triethyl orthoformate was removed under vacuum. The solid residue obtained was crystallized from a suitable solvent.

Method B. General Procedure for the Preparation of 1,2,4-Triazolo-[2,3-*c*]thieno[3,2-*e*]pyrimidines (**2a-2j**).

A solution of 4-hydrazinothieno[2,3-*d*]pyrimidine (0.02 mole) in excess of formic acid (30 ml.) was refluxed on an oil bath for 2 hours. The mixture was concentrated under reduced pressure. On cooling, the solid obtained was filtered and dried. Crystallization from a suitable solvent afforded 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine.

Method C. Synthesis of 1,2,4-Triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines with Formic Acid at 45-50° **1a-1b** and **1d**.

A solution of 4-hydrazinothieno[2,3-*d*]pyrimidine (0.02 mole) in formic acid (30 ml.) was warmed on a water bath at 45-50° for 6 hours. The solution was cooled and poured into ice-water mixture. The precipitate obtained was filtered, washed free of acid and dried. Crystallization from a suitable solvent yielded the corresponding 1,2,4-triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidine.

Method D. General Procedure for the Preparation of 3-Methyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines (**9a-9c**).

A mixture of 4-hydrazinothieno[2,3-*d*]pyrimidine (0.01 mole) and triethyl orthoacetate (30 ml.) was refluxed for 4-5 hours. Excess of triethyl orthoacetate was removed under vacuum. The residue on crystallization gave the corresponding 3-methyl-1,2,4-triazolo[4,3-*c*]-thieno[3,2-*e*]pyrimidine.

Method E. General Procedure for the Preparation of 2-Methyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines (**10a-10c**).

A mixture of 4-hydrazinothieno[2,3-*d*]pyrimidine (0.01 mole) and acetic acid (20 ml.) was refluxed for 4-5 hours. After the removal of the excess acetic acid in vacuum, water (30 ml.) was added to the residue and the prodect was filtered and crystallized from a suitable solvent.

3-Amino-4-imino-2-methyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**5**).

2-Amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3.2 g.) was refluxed with triethyl orthoacetate (20 ml.) for 4 hours. Excess of triethyl orthoacetate was removed under vacuum. To the residue was added a mixture of hydrazine hydrate (99%; 5 ml.) and ethanol (15 ml.) with stirring. The mixture was allowed to stand overnight at room temperature. The yellow solid obtained was filtered and crystallized from ethanol, m.p. 176-178°, yield 1.8 g. (50%); uv (ethanol): λ max 219 (4.64), 250 (4.62), 275 (4.21), 312 nm (4.24); ir (nujol): cm^{-1} 3320, 3140 (NH), 1600 (C=N).

Anal. Calcd. for $C_{11}H_{14}N_4S$: C, 56.41; H, 5.98. Found: C, 56.14; H, 6.29.

1,2,4-Triazolo[2,3-*c*]-5-methyl-8,9,10,11-tetrahydrobenzo[*b*]thieno[3,2-*e*]-pyrimidine (**2a**).

3-Amino-4-imino-2-methyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidine (2.4 g., 0.01 mole) was refluxed with excess of triethyl orthoformate (30 ml.) for 4 hours. Excess of reagent was removed under vacuum. The residue obtained was crystallized from ethanol, m.p. 156-158°, yield 1.9 g. (78%); uv (ethanol): λ max 250 (4.65), 292 nm (4.38); ir (nujol): cm^{-1} 2900 (CH), 1620 (C=N), 1420, 1360, 1270, 1200, 770, 720; nmr (deuteriochloroform): δ 1.9 (m, 4H, CH_2 at C-9 and C-10), 2.95 (m, CH_2 at C-8 and C-11 and CH_3 at C-5), 8.2 (s, H at C-3); ms: molecular weight calcd. 244; found 244.

Anal. Calcd. for $C_{12}H_{12}N_4S$: C, 59.01; H, 4.95. Found: C, 59.32; H, 5.15.

This compound was identical with the product obtained from **6** by the method B (tlc, no depression in mixed melting point and superimposible ir).

Conversion of 1,2,4-Triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines to 1,2,4-Triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines.

A mixture of 1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine **1a, 1d, 1f** or **9b** (0.01 mole) and **p**-toluenesulfonic acid (0.01 mole) in excess of benzene (30 ml.) was refluxed for 4 hours. The course of the reaction was monitored at regular intervals by micro tlc using benzene-methanol (8:1) as solvent system. About 95% conversion was observed at the end of 3.5 hours as indicated by the intensity of the spot corresponding to the 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine. The mixture was cooled and filtered. Filtrate was concentrated and the solid obtained was crystallized from a suitable solvent to yield the corresponding 1,2,4-triazolo[2,3-*c*]-thieno[3,2-*e*]pyrimidine **2a, 2d, 2f** and **10b**.

The rearranged triazoles were found to be identical with those triazoles obtained by the direct cyclization employing the method B or method E.

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