# Studies on the Synthesis and Interconversion of Isomeric Triazolothienopyrimidines. Part II. Effect of 5-Substituents on the Dimroth Rearrangement of 1,2,4-Triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines



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The triazolothienopyrimidines obtained by the cyclization of 4-hydrazino-2-phenylthieno[2,3-*d*]pyrimidines with triethyl orthoformate or formic acid presumed to be the triazolo[2,3-*c*] isomers are now assigned the 5-phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine structure. While these [4,3-*c*]triazoles resist isomerization under acidic conditions, they undergo isomerization to 5-phenyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines under basic conditions.

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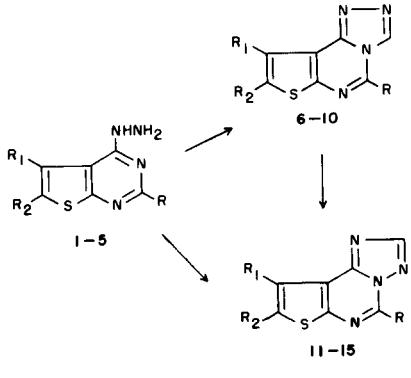
Earlier, we have observed that the cyclization of 4-hydrazinothieno[2,3-*d*]pyrimidines **1** with triethyl orthoformate at reflux yields 1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidines **6** and the cyclization of **1** with formic acid at reflux gives the isomeric 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines **11**. While the 5-unsubstituted-, 5-alkyl- and 5-aralkyltriazolo[4,3-*c*]thienopyrimidines **6** were found to undergo isomerization to [2,3-*c*] isomers **11** under acidic, as well as, basic conditions, the 5-styryl-1,2,4-triazolo[4,3-*c*]thienopyrimidine **7** resists isomerization to **12** under acidic conditions [2,3].

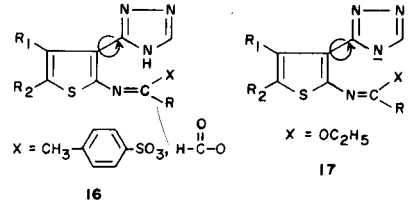



| | |
|---|---|
| 1,6,11 | R = H, Alkyl, Aralkyl, $R_1$ = $CH_3$, $C_6H_5$, $R_2$ = $CH_3$, H, $R_1R_2$ = $-(CH_2)_4-$ |
| 2,7,12 | R = $C_6H_5CH{=}CH-$, $R_1R_2$ = $-(CH_2)_4-$ |
| 3,8,13 | R = $C_6H_5$, $R_1R_2$ = $-(CH_2)_4-$ |
| 4,9,14 | R = $C_6H_5$, $R_1$ = $R_2$ = $CH_3$ |
| 5,10,15 | R = $R_1$ = $C_6H_5$, $R_2$ = H |

The triazolothienopyrimidines obtained by the cyclization of 4-hydrazino-2-phenylthieno[2,3-*d*]pyrimidines **3-5** with triethyl orthoformate or formic acid, were earlier assigned 1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine structure because of their failure to isomerize under acid catalysis [2]. However, in the light of recent observations [3], it appears that these triazoles could be the [4,3-*c*] isomers **8-10**, which resist acid catalyzed isomerization. Indeed, it has now been found that the triazoles **8-10** could be made to isomerize under basic conditions to yield a new set of triazoles **13-15**. Hence the compounds **8-10** are now assigned 5-phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine structure and triazoles **13-15**, obtained by the base catalysed isomerization of **8-10**, are assigned 5-phenyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine structure.

While the triazoles **8-10** exhibit the triazole proton signal at $\delta$ 8.9, the triazoles **13-15** give the proton signal at around $\delta$ 8.4. This is in accordance with our earlier observation that the triazole proton of triazolo[4,3-*c*] isomers are more deshielded than that of [2,3-*c*] isomers [2].

The isomerization of triazolo[4,3-*c*]thienopyrimidines to the [2,3-*c*] isomers presumably proceeds *via* the formation of ring opened intermediates **16** or **17** in the presence of acids, such as *p*-toluenesulfonic acid or formic acid or bases like sodium ethoxide.




The inability of 5-phenyl- and 5-styryl substituted triazolo[4,3-*c*]thienopyrimidines to isomerize under acidic conditions can be rationalized as due to the stabilization of **18**

Scheme I

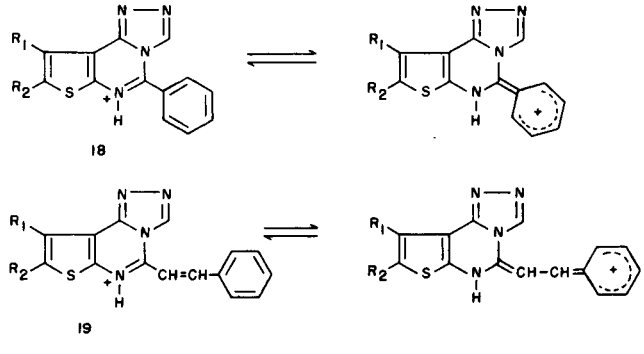
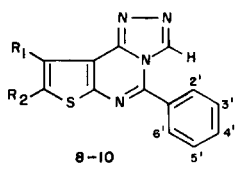
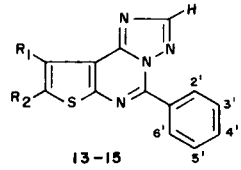


Table 1

5-Phenyl-1,2,4-triazolothieno[3,2-*e*]pyrimidines



8-10



13-15

| Compound No. | $R_1$ | $R_2$ | Mp °C | % Yield | Recrystallization Solvent [a] | Molecular Formula | Molecular Weight | Microanalysis Calcd./Found %C | %H |
|---|---|---|---|---|---|---|---|---|---|
| **8** | -$(CH_2)_4$- | | 207-210 | 60 | M-C | $C_{17}H_{14}N_4S$ | 306 [b] | 66.64 | 4.61 |
| | | | | | | | | 66.45 | 4.85 |
| **9** | $CH_3$ | $CH_3$ | 229-231 | 90 | M-C | $C_{15}H_{12}N_4S$ | 280 | 64.26 | 4.31 |
| | | | | | | | | 64.06 | 4.72 |
| **10** | $C_6H_5$ | H | 233-235 | 63 | M-C | $C_{19}H_{12}N_4S$ | 328 | 69.49 | 3.68 |
| | | | | | | | | 69.71 | 4.00 |
| **13** | -$(CH_2)_4$- | | 146-148 | 66 | PE | $C_{17}H_{14}N_4S$ | 306 [b] | 66.64 | 4.61 |
| | | | | | | | | 67.07 | 4.79 |
| **14** | $CH_3$ | $CH_3$ | 191-193 | 54 | PE-B | $C_{15}H_{12}N_4S$ | 280 | 64.26 | 4.31 |
| | | | | | | | | 64.02 | 4.34 |
| **15** | $C_6H_5$ | H | 176-178 | 78 | PE | $C_{19}H_{12}N_4S$ | 328 | 69.49 | 3.68 |
| | | | | | | | | 69.19 | 4.13 |

[a] C = Chloroform, M = Methanol, PE = Petroleum Ether (60-80°), B = Benzene. [b] Molecular weight determined by mass spectra.

Table 2

Spectral Data of 5-Phenyl-1,2,4-triazolothieno[3,2-*e*]pyrimidines

| Compound No. | UV (Ethanol or Methanol) λ max (log ε) | MS: m/e | $^1$H-NMR (Deuteriochloroform/TMS) δ ppm [c] |
|---|---|---|---|
| **8** | 232 (4.57), 335 (4.44) | 306 ($M^+$), 291, 278, 264, 251, 202, 175, 160 | 2.0 (4H, m, C*H*$_2$ at 9 and 10), 3.08 (4H, m, C*H*$_2$ at 8 and 11), 7.6 (3H, m, *H* at 3′, 4′ and 5′ at $C_6H_5$ of $C_5$), 7.96 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$), 8.96 (1H, s, triazole proton) |
| **9** | 230 (4.57), 335 (4.45) | — | 2.6 (3H, s, C*H*$_3$ at $C_9$), 2.8 (3H, s, C*H*$_3$ at $C_8$), 7.7 (3H, m, *H* at 3′, 4′ and 5′ of $C_6H_5$ at $C_5$), 7.95 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$), 9.05 (1H, s, triazole proton) |
| **10** | 230 (4.63), 332 (4.47) | — | 7.53 (9H, m, *H* at 3′, 4′ and 5′ of $C_6H_5$ at $C_5$, $C_6H_5$ at $C_9$ and *H* at $C_8$), 7.87 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$), 8.95 (1H, s, triazole proton) |
| **13** | 218 (4.31), 249 (4.29), 320 (4.29) | 306 ($M^+$), 291, 279, 265, 251, 202 | 1.98 (4H, m, C*H*$_2$ at 9 and 10), 3.03 (4H, m, $CH_2$ at 8 and 11), 7.6 (3H, m, *H* at 3′, 4′ and 5′ of $C_6H_5$ at $C_5$), 8.4 (1H, s, triazole proton), 8.57 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$) |
| **14** | 222 (4.32), 249 (4.33), 326 (4.31) | — | 2.53 (3H, s, C*H*$_3$ at $C_9$), 2.7 (3H, s, C*H*$_3$ at $C_8$), 7.51 (3H, m, *H* at 3′, 4′ and 5′ of $C_6H_5$ at $C_5$), 8.33 (1H, s, triazole proton), 8.47 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$) |
| **15** | 222 (4.43), 249 (4.37), 321 (4.23) | — | 7.67 (9H, m, *H* at 3′, 4′ and 5′ of $C_6H_5$ at $C_5$, $C_6H_5$ at $C_9$ and *H* at $C_8$), 8.4 (1H, s, triazole proton), 8.83 (2H, m, *H* at 2′ and 6′ of $C_6H_5$ at $C_5$) |

[c] Line shapes: s = singlet, m = multiplet.

and **19** through the delocalization of +ve charge on pyrimidine ring, thereby rendering the nucleophilic ring opening of the pyrimidine system difficult (Scheme I).

In general, the triazolo[4,3-*c*]thienopyrimidines appear to possess an intrinsic tendency to isomerize to [2,3-*c*] isomers, probably because of the thermodynamic stability of the latter.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Ultra-violet absorption spectra were determined using Beckman Model 25 spectrophotometer. Infrared spectra were recorded on 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 ionizing beam, using direct insertion probe.

Base Catalysed Isomerization of 5-Phenyl-1,2,4-triazolo[4,3-*c*]thieno-[3,2-*e*]pyrimidines **8-10** to 5-Phenyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidines **13-15**.

A mixture of 5-phenyl-1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine (0.01 mole) and ethanol (30 ml) containing sodium ethoxide (10-15 mg) was warmed on a waterbath for 30 minutes and allowed to stand at room temperature for 12 hours. The solid obtained was filtered and dried. Crystallization from a suitable solvent yielded 5-phenyl-1,2,4-triazolo[2,3-*c*]thieno[3,2-*e*]pyrimidine.

## REFERENCES AND NOTES

[1] To whom correspondence regarding this paper should be addressed.

[2] C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan and V. S. Bhadti, *J. Heterocyclic Chem.*, **18**, 43 (1981).

[3] C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan and V. S. Bhadti, *J. Heterocyclic Chem.*, **22** 825 (1985).

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