A Convenient Synthesis of New 2-Phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine Derivatives by Dimroth Rearrangement

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The heterocyclic compounds containing 1,2,4-triazole moiety continue to attract considerable interest because of their broad biological activities such as antifungal, bactericidal, antitumor, and anti-inflammatory agents. Furthermore, it has been noticed that introduction of an additional ring to the triazolopyrimidine system which is one of the fused 1,2,4-triazole compound tends to exert profound influence in conferring new biological activities in these molecules. For instance, thienotriazolopyrimidinone 1 and pyrazolotriazolopyrimidine 2 derivatives of tricyclic heterocyclic compounds as shown in Fig. 1 have been explored for xanthine oxidase inhibitor, and adenosine A1/A2A or A2A/A3 receptor antagonists, respectively.†,‡ And, triazoloquinazolone 3 and its analogs were also known to have antibacterial and H1-antihistaminic activity.§

We have recently designed and synthesized a series of thienotriazolopyrimidine compounds 4 of potential biological interest.† In continuation of our works for biologically active heterocyclic compounds we describe herein the convenient synthesis of 2-phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives 5 as a new ring system from 3-phenylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines 4 by Dimroth-type rearrangement.

The compounds 4 were prepared through a series of reactions starting with 2-aminothiophene-3-carbonitrile (6) according to the procedure we have previously reported.† Reaction of 6 with triethyl orthoformate and the successive hydrazine hydrate afforded 4-hydrazinothieno[2,3-d]pyrimidine. The hydrazone derivatives were synthesized by condensation of hydrazine compounds with the corresponding benzaldehydes in toluene in the presence of catalytic amount of p-toluene sulfonic acid. The oxidative cyclization of the resultant hydrazone derivatives using iodobenzene diacetate gave 4.

When each of 4 was heated in ethanol in the presence of sodium acetate, they isomerized to the thermodynamically...
In order to provide a decisive evidence for the exact structure of 5, the product 5a was compared with authentic sample prepared by alternative syntheses.\(^{11}\) Treatment of 7 with benzoylhydrazine in the presence of a catalytic amount of p-toluene sulfonic acid in refluxing DMF and followed by dehydration gave the authentic product 5a. This was identical in all respects (mp, IR, \(^1\)H NMR and MS spectra) with one obtained from sodium acetate (base) catalyzed Dimroth rearrangement of 4a. This finding confirms the Dimroth rearrangement of 4 into 5. The conversion of 4 into 5 is analogous to rearrangement of [1,2,4]triazolo[4,3-c]pyrimidines in alkali to the isomeric [1,2,4]triazolo[1,5-c]pyrimidines.\(^{12}\) This rearrangement is also consistent with those reported in recent reports, which were the rearrangements of thiolo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-5(1H)-ones,\(^3\) pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines and 1,4-disubstituted [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones.\(^{5a,13}\)

In conclusion, we found a convenient and reliable synthesis of 2-phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives 5 via rearrangement of 3-phenylthieno [3,2-e][1,2,4]triazolo[4,3-c]pyrimidines 4.

### EXPERIMENTAL

All products were characterized by IR, \(^1\)H NMR, MS and elemental analysis. Melting points were measured by using the capillary tubes on Büchi apparatus and are uncorrected. Each compound of the reactions was checked on thin-layer chromatography of Merck Kieselgel 60F254 and purified by column chromatography using Merck silica gel (70 - 230 mesh). IR spectra were recorded on the FT-IR Brucker Tensor 27. The \(^1\)H NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (300 MHz) with MeSi as internal standard and chemical shifts are given in ppm (\(\delta\)). Electron ionization mass spectra were recorded on a HP 59580 B spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

#### General procedure for the preparation of 2-phenylthieno [3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives (5).

To a solution of each 3-phenylthieno[3,2-e][1,2,4]triazolo[4,3-c] pyrimidine 4 (1 mmol) in ethanol (30 mL) was added sodium acetate (0.164 g, 2 mmol) and the mixture was refluxed for 5 h and cooled. The precipitated solid was filtered, washed with water, dried and finally crystallized from ethanol to give the respective 2-phenylthieno[3,2-e][1,2,4]triazolo [1,5-c]pyrimidine 5.

2-Phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5a). Yield 76%; mp 184 - 186 °C; IR (KBr): 3062, 1631 cm

\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 9.27 (s, 1H, pyrimidine-H), 8.37-8.33 (m, 2H, phenyl, H-2 and H-6), 7.88 (d, \(J = 5.9\) Hz, 1H,
thiophene), 7.70 (d, J = 5.9 Hz, thiophene), 7.56-7.52 (m, 3H, phenyl, H-3 and H-5); MS: (m/z) 252 (M⁺, 100), 149 (10), 134 (17), 118 (20), 95 (10), 77 (8). Anal. Calcd. for C₁₅H₁₁N₄S: C, 56.89; H, 3.20; N, 19.46.

2-(4-Chlorophenyl)thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5b). Yield 78%; mp 265 - 267 °C; IR (KBr): 3040, 1622 cm⁻¹; ¹H NMR (CDCl₃): δ 9.25 (s, 1H, pyrimidine-H), 8.29 (d, 2H, phenyl, H-2 and H-6), 7.86 (d, J = 5.9 Hz, 1H, thiophene), 7.71 (d, J = 5.9 Hz, thiophene), 7.51 (d, 2H, phenyl, H-3 and H-5); MS: (m/z) 287 (M⁺, 100), 149 (22), 134 (15). Anal. Calcd. for C₁₅H₁₁N₄S: C, 54.45; H, 2.46; N, 19.54. Found: C, 54.60; H, 2.30; N, 19.40.

2-P-Tolythieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5e). Yield 62%; mp 217 - 218 °C; IR (KBr): 3040, 1626, 1330 cm⁻¹; ¹H NMR (CDCl₃): δ 9.24 (s, 1H, pyrimidine-H), 8.23 (d, 2H, phenyl, H-2 and H-6), 7.87 (d, J = 5.9 Hz, 1H, thiophene), 7.69 (d, J = 5.9 Hz, thiophene), 7.54 (d, 2H, phenyl, H-3 and H-5); MS: (m/z) 266 (M⁺, 100), 149 (25), 134 (10), 117 (10), 91 (9). Anal. Calcd. for C₁₅H₁₁N₄S: C, 63.14; H, 3.78; N, 21.04. Found: C, 63.30; H, 3.70; N, 21.22.

2-(4-Methoxyphenyl)thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5d). Yield 60%; mp 236 - 238 °C; IR (KBr): 3050, 2955, 1630, 1370 cm⁻¹; ¹H NMR (CDCl₃): δ 9.24 (s, 1H, pyrimidine-H), 8.27 (d, 2H, phenyl, H-2 and H-6), 7.86 (d, J = 5.9 Hz, 1H, thiophene), 7.68 (d, J = 5.9 Hz, thiophene), 7.05 (d, 2H, phenyl, H-3 and H-5), 3.90 (s, 3H, Me); MS: (m/z) 282 (M⁺, 100), 149 (12), 134 (19). Anal. Calcd. for C₁₅H₁₄O₃N₄S: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.69; H, 3.43; N, 19.99.

2-(4-Bromophenyl)thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5i). Yield 70%; mp 220 - 222 °C; IR (KBr): 3090, 2975, 1610, 1375 cm⁻¹; ¹H NMR (CDCl₃): δ 9.26 (s, 1H, pyrimidine-H), 8.17-8.13 (m, 2H, phenyl, H-4 and H-6), 7.88 (d, J = 5.9 Hz, 1H, thiophene), 7.69 (d, J = 5.9 Hz, thiophene), 7.42 (t, 1H, phenyl, H-5), 7.34 (d, 1H, phenyl, H-3), 2.48 (s, 3H, Me); MS: (m/z) 282 (M⁺, 100), 149 (18), 134 (15). Anal. Calcd. for C₁₅H₁₁BrN₄S: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.71; H, 3.66; N, 20.01.

REFERENCES

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