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단신

Dimroth 재배열을 이용한 새로운 2-Phenylthieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 유도체의 편리한 합성

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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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주제어: 딤로스 재배열, 싸이에노트리아졸로피리미딘 유도체, 하이드라존, 헤테로고리

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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.[1-4] 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 A_1/A_{2A} or A_{2A}/A_3 receptor antagonists, respectively.[5,6] And, triazoloquinazolinone **3** and its analogs were also known to have antibacterial and H_1-antihistaminic activity.[7,8]

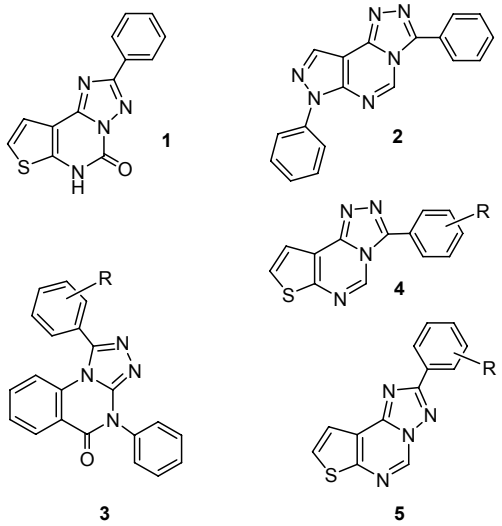
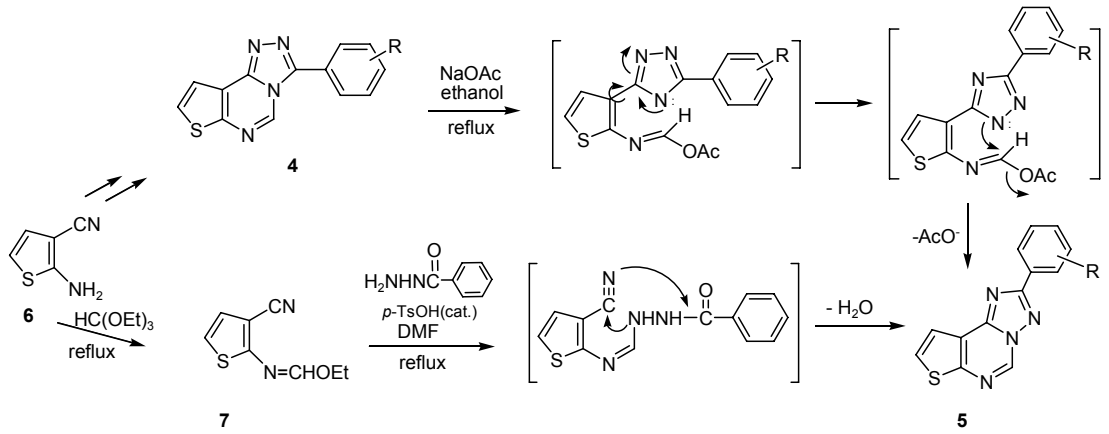


***Fig*. 1**

We have recently designed and synthesized a series of thienotriazolopyrimidine compounds **4** of potential biological interest.[9] In continuation of our works for biologically active heterocyclic compounds[10] 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.[9] 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



***Scheme* 1**

more stable compounds **5** *via* successive ring opening and ring closing by Dimroth-type rearrangement (*Scheme* 1). For instance, the reaction of **4a** (1 mmol) with sodium acetate (2 mmol) in refluxing ethanol for 5 h gave only one product, **5a** in 76% yield. The structures of all new compounds **5** were confirmed by elemental analyses and spectral (MS, ^{1}H NMR) data. Especially, each isomer of **4** and **5** was distinguishable by ^{1}H NMR spectra. The most prominent peak of **4a**, for example, was observed at δ 9.02 as a singlet attributed to the pyrimidine proton, whereas the similar singlet of **5a** was observed at δ 9.27 in more down field. The relatively down field region of pyrimidine proton in **5a** can be attributed to proximity of the nitrogen atom rearranged in the triazole ring.

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 refuxing 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-*a*]pyrimidines in alkali to the isomeric [1,2,4]triazolo[1,5-*a*]pyrimidines.[12] This rearrangement is also consistent with those reported in recent reports, which were the rearrangements of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(1*H*)-ones,[5] 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(4*H*)-ones.[6a,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 60F_{254} 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 Me_4Si as internal standard and chemical shifts are given in ppm (δ). 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 ($CDCl_3$): δ 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, H-4 and H-5); MS: (*m*/*z*) 252 (M^+, 100), 149 (10), 134 (17), 118 (20), 95 (10), 77 (8). *Anal.* Calcd. for $C_{13}H_8N_4S$: C, 61.89; H, 3.20; N, 22.21. Found: C, 61.71; H, 3.32; N, 22.05.

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 ($CDCl_3$): δ 9.26 (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 $C_{13}H_7ClN_4S$: C, 54.45; H, 2.46; N, 19.54. Found: C, 54.60; H, 2.30; N, 19.40.

2-*p*-Tolylthieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5c). Yield 62%; mp 217 - 218 °C; IR (KBr): 3040, 2946, 1626, 1330 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H, pyrimidine-H), 8.23 (d, 2H, phenyl, H-2 and H-6), 7.87 (d, *J* = 5.9 Hz, 1H, thiophene), 7.68 (d, *J* = 5.9 Hz, thiophene), 7.34 (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 $C_{14}H_{10}N_4S$: 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 ($CDCl_3$): 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 $C_{14}H_{10}N_4OS$: 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 (5e). Yield 70%; mp 244 - 246 °C; IR (KBr): 3030, 1600 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.73 (s, 1H, pyrimidine-H), 8.28 (d, 2H, phenyl, H-2 and H-6), 8.10 (d, *J* = 5.9 Hz, 1H, thiophene), 7.88 (d, *J* = 5.9 Hz, thiophene), 7.79 (d, 2H, phenyl, H-3 and H-5); MS: (*m*/*z*) 331 (M^+). *Anal.* Calcd. for $C_{13}H_7BrN_4S$: C, 47.14; H, 2.13; N, 16.92. Found: C, 47.29; H, 2.25; N, 16.80.

2-(3-Chlorophenyl)thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5f). Yield 74%; mp 247 - 249 °C; IR (KBr): 3045, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.26 (s, 1H, pyrimidine-H), 8.36 (s, 1H, phenyl, H-2), 8.23 (d, 1H, phenyl, H-6), 7.87 (d, *J* = 5.9 Hz, 1H, thiophene), 7.71 (d, *J* = 5.9 Hz, thiophene), 7.51-7.46 (m, 2H, phenyl, H-4 and H-5); MS: (*m*/*z*) 287 (M^+, 100), 149 (15), 134 (20). *Anal.* Calcd. for $C_{13}H_7ClN_4S$: C, 54.45; H, 2.46; N, 19.54. Found: C, 54.59; H, 2.57; N, 19.60.

2-*m*-Tolylthieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5g). Yield 63%; mp 193 - 195 °C; IR (KBr): 3040, 1635, 1375 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.33 (s, 1H, pyrimidine-H), 8.20 (d, 1H, phenyl, H-6), 7.89 (d, *J* = 5.9 Hz, 1H, thiophene), 7.68 (d, *J* = 5.9 Hz, thiophene), 7.53 (t, 1H, phenyl, H-5), 7.17-7.09 (m, 2H, phenyl, H-2 and H-4); MS: (*m*/*z*) 266 (M^+, 100), 149 (15). *Anal.* Calcd. for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04. Found: C, 63.01; H, 3.67; N, 21.18.

2-(3-Bromophenyl)thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5h). Yield 69%; mp 246 - 248 °C; IR (KBr): 3064, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.27 (s, 1H, pyrimidine-H), 8.52 (s, 1H, phenyl, H-2), 8.28 (d, 1H, phenyl, H-6), 7.86 (d, *J* = 5.9 Hz, 1H, thiophene), 7.73 (d, *J* = 5.9 Hz, thiophene), 7.65 (d, 1H, phenyl, H-4), 7.41 (t, 1H, phenyl, H-5); MS: (*m*/*z*) 331 (M^+, 100), 134 (20). *Anal.* Calcd. for $C_{13}H_7BrN_4S$: C, 47.14; H, 2.13; N, 16.92. Found: C, 47.32; H, 2.02; N, 17.10.

2-(2-Methoxyphenyl)thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5i). Yield 56%; mp 220 - 222 °C; IR (KBr): 3090, 2975, 1610, 1375 cm^{-1}; ^1H NMR ($CDCl_3$): 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 $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.71; H, 3.66; N, 20.01.

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