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단신
새로운 고리 시스템인 2-Phenylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 유도체의 손쉬운 합성

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Facile Synthesis of 2-Phenylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine Derivatives as a New Ring System

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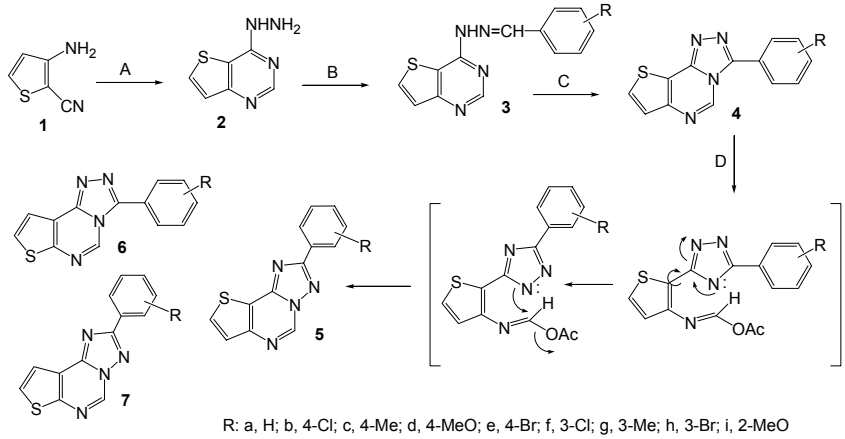
INTRODUCTION

Much attention has been recently paid to the synthesis of some thieno[1,2,4]triazolopyrimidines and thieno[1,2,4]triazolopyrimidinones because of their biological activities.[1-4] With this in mind and in continuation of our recent work on the synthesis of 2-phenylthieno[3,2-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine derivatives **7**[5] we describe here a facile synthesis of 2-phenylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives **5** that have not been reported hitherto as a new ring system. Previous observations revealed that the thieno [3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **6** can isomerizes in the presence of base to the thermodynamically more stable thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **7** by Dimroth-type rearrangement. We, therefore, decided to apply this methodology also to the synthesis of **5** from **4**.

The compounds **4** were prepared through a series of reaction starting with 3-aminothiophene-2-carbonitrile (**1**) according to the modified procedure we have previously reported (*Scheme* 1).[1] The required starting material **1** was obtained by adopting the new synthetic method.[6] Reaction of **1** with triethyl orthoformate and the successive hydrazine hydrate gave 4-hydrazinothieno[3,2-*d*]pyrimidine (**2**). The hydrazone derivatives **3** were synthesized by condensation of hydrazine compound **2** with the corresponding benzaldehydes in refluxing ethanol in the presence of catalytic amount of piperidine. The oxidative cyclization of the resultant hydrazone derivatives **3** to **4** was achieved using alumina-supported calcium hypochlorite ($Ca(OCl)_2/Al_2O_3$ = 1:1, grounded mixture) as a new oxidant. For instance, a maximum yield of 73% for **4a** in 1 h was achieved with 1:3 molar ratio of hydrazone to calcium hypochlorite. The use of alumina-supported calcium hypochlorite as a heterogeneous oxidant in this reaction has advantage of enhanced reaction rate and yield, simple work-up, low cost, and eco-friendly reagent when compared to other oxidants such as bromine,[7] lead tetraacetate,[8] iodobenzene diacetate[1,9] or copper dichloride.[10]

When each of **4** was treated with sodium acetate in refluxing ethanol, it underwent a Dimroth-type rearrangement to give compounds **5** through a sequence of ring opening and ring closure reaction. For instance, the reaction of **4a** (1 mmol) with sodium acetate (2 mmol) in refluxing ethanol for 5 h afforded only one product, **5a** in 68% yield. The structures of all new compounds **5** were identified by elemental analyses and spectral data. The results are summarized in *Table* 1. It was noticed that the two isomeric **4** and **5** showed no appreciable differences in the fragmentation pattern of MS spectra, however, the ^{1}H NMR spectra of **5** revealed that the most prominent pyrimidine proton showed signal little more downfield than the one of their isomeric **4**. These results were in agreement with those reported in earlier report.[5] The conversion of **4** into **5** is also analogous to rearrangement of thieno [2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones in base to the isomeric thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones.[4]

In conclusion, we report a facile synthesis of 2-phenyl-



***Scheme* 1.** Reagents and conditions; (A) (i) $HC(OEt)_3$, reflux (ii) hydrazine hydrate/ethanol, reflux; (B) benzaldehydes, piperidine/ethanol, reflux; (C) $Ca(OCl)_2$-Al_2O_3/methylene chloride, rt; (D) NaOAc/ethanol, reflux

***Table* 1.** Preparation of compounds **5** from **4**

Entry	R	Product	Mp (°C)	Yield (%)[a]
1	H	**5a**	105 - 107	68
2	4-Cl	**5b**	250 - 252	70
3	4-Me	**5c**	203 - 205	55
4	4-MeO	**5d**	201 - 203	62
5	4-Br	**5e**	207 - 208	68
6	3-Cl	**5f**	140 - 142	63
7	3-Me	**5g**	164 - 166	60
8	3-Br	**5h**	134 - 136	65
9	2-MeO	**5i**	127 - 129	50

[a]Isolated yields.

thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives **5** *via* rearrangement of 3-phenylthieno[2,3-*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 [2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives (5)

To a solution of each 3-phenylthieno[2,3-*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[2,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidine **5**.

2-Phenylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5a)

Yield 68%; mp 105 - 107 °C; IR (KBr): 3045, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.32 (s, 1H, H-4), 8.36-8.33 (m, 2H, H-2' and H-6'), 7.88 (d, 1H, J = 5.9 Hz, H-7), 7.65 (d, 1H, J = 5.9 Hz, H-6), 7.55-7.52 (m, 3H, H-3', H-4' and H-5'); MS: (*m*/*z*) 252 (M^+, 100), 149 (15), 134 (20), 118 (16). *Anal.* Calcd. for $C_{13}H_8N_4S$: C, 61.89; H, 3.20; N, 22.21. Found: C, 61.69; H, 3.39; N, 22.48.

2-(4-Chlorophenyl)thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine (5b)

Yield 70%; mp 250 - 252 °C; IR (KBr): 3052, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.30 (s, 1H, H-4), 8.29 (d, 2H, H-2' and H-6'), 7.88 (d, J = 5.9 Hz, 1H, H-7), 7.65 (d, J = 5.9 Hz, 1H, H-6), 7.51 (d, 2H, H-3' and H-5'); MS: (*m*/*z*) 287 (M^+, 100), 149 (30), 134 (22). *Anal.* Calcd. for $C_{13}H_7ClN_4S$: C, 54.45; H, 2.46; N, 19.54. Found: C, 54.29; H, 2.31; N, 19.71.

2-*p*-Tolylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5c)

Yield 55%; mp 203 - 205 °C; IR (KBr): 3050, 2973, 1620,

1370 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, H-4), 8.23 (d, 2H, H-2' and H-6'), 7.86 (d, *J* = 5.9 Hz, 1H, H-7), 7.63 (d, *J* = 5.9 Hz, 1H, H-6), 7.34 (d, 2H, H-3' and H-5'), 2.44 (s, 3H, Me); MS: (*m*/*z*) 266 (M^+, 99), 149 (35), 134 (20). *Anal.* Calcd. for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04. Found: C, 63.30; H, 3.59; N, 21.22.

2-(4-Methoxyphenyl)thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5d)

Yield 62%; mp 201 - 203 °C; IR (KBr): 3044, 2980, 1622, 1375 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.27(s, 1H, H-4), 8.26 (d, 2H, H-2'and H-6'), 7.85 (d, *J* = 5.9 Hz, 1H, H-7), 7.62 (d, *J* = 5.9 Hz, 1H, H-6), 7.03 (d, 2H, H-3' and H-5'), 3.89 (s, 3H, OMe); MS: (*m*/*z*) 282 (M^+, 100), 149 (15), 134(22). *Anal.* Calcd. for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.44; H, 3.66; N, 19.93.

2-(4-Bromophenyl)thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5e)

Yield 68%; mp 207 - 208 °C; IR (KBr): 3033, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, H-4), 8.22 (d, 2H, H-2' and H-6'), 7.88 (d, *J* = 5.9 Hz, 1H, H-7), 7.69 (d, *J* = 5.9 Hz, 1H, H-6), 7.65 (d, 2H, H-3' and H-5'); MS: (*m*/*z*) 331 (M^+, 98), 149 (12), 134 (10). *Anal.* Calcd. for $C_{13}H_7BrN_4S$: C, 47.14; H, 2.13; N, 16.92. Found: C, 46.99; H, 2.34; N, 17.14.

2-(3-Chlorophenyl)thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5f)

Yield 63%; mp 140 - 142 °C; IR (KBr): 3035, 1629 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, H-4), 8.55 (s, 1H, H-2'), 8.04 (m, 1H, H-6'), 7.72 (d, *J* = 5.9 Hz, 1H, H-7), 7.53 (d, *J* = 5.9 Hz, 1H, H-6), 7.46-7.39 (m, 2H, H-4' and H-5'); MS: (*m*/*z*) 287 (M^+, 100), 149 (16), 134 (20). *Anal.* Calcd. for $C_{13}H_7ClN_4S$: C, 54.45; H, 2.46; N, 19.54. Found: C, 54.66; H, 2.30; N, 19.69.

2-*m*-Tolylthieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5g)

Yield 60%; mp 164 - 166 °C; IR (KBr): 3036, 1625, 1375 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (s, 1H, H-4), 8.18-8.14 (m, 2H, H-2' and H-6'), 7.87 (d, *J* = 5.9 Hz, 1H, H-7), 7.64 (d, *J* = 5.9 Hz, 1H, H-6), 7.42 (t, 1H, H-5'), 7.33 (d, 1H, H-4'), 2.48 (s, 3H, Me); MS: (*m*/*z*) 266 (M^+, 100), 149 (10). *Anal.* Calcd. for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04. Found: C, 63.29; H, 3.65; N, 21.11.

2-(3-Bromophenyl)thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5h)

Yield 65%; mp 134 - 136 °C; IR (KBr): 3034, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.29 (s, 1H, H-4), 8.58 (s, 1H, H-2'), 8.05 (d, 1H, H-6'), 7.74 (d, *J* = 5.9 Hz, 1H, H-7), 7.59 (d, *J* = 5.9 Hz, 1H, H-6), 7.54 (d, 1H, H-4'), 7.36 (t, 1H, H-5'); MS: (*m*/*z*) 331 (M^+, 100), 149 (11), 134 (20). *Anal.* Calcd. for $C_{13}H_7BrN_4S$: C, 47.14; H, 2.13; N, 16.92. Found: C, 47.28; H, 2.26; N, 17.11.

2-(2-Methoxyphenyl)thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (5i)

Yield 50%; mp 127 - 129 °C; IR (KBr): 3030, 2975, 1620, 1375 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.28 (s, 1H, H-4), 8.14-8.10 (m, 2H, H-4' and H-6'), 7.88 (d, *J* = 5.9 Hz, 1H, H-7), 7.55 (d, *J* = 5.9 Hz, 1H, H-6), 7.33 (t, 1H, H-5'), 7.24 (d, 1H, H-3'), 2.47 (s, 3H, OMe); MS: (*m*/*z*) 282 (M^+, 100), 149 (14), 134 (18). *Anal.* Calcd. for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.85. Found: C, 59.69; H, 3.42; N, 19.62.

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