Jae Woo Park and Yang-Heon Song*

Synthesis of thienopyrimidine-pyrazolo[3,4-*b*] pyridine hybrids

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Abstract: New hybrid compounds, thienopyrimidinyl-1*H*-pyrazolo[3,4-*b*]pyridine derivatives, were efficiently synthesized by the three-component reaction of 3-phenyl-1-(thienopyrimidin-4-yl)-1*H*-pyrazol-5-amine, benzoylacetonitrile and an aromatic aldehyde in the presence of $FeCl_3$ on basic alumina.

Keywords: basic alumina; iron(III) chloride; pyrazolo[3,4-*b*]pyridine; thienopyrimidine; three-component reaction.

Introduction

Pyrazolo[3,4-*b*]pyridines have been reported to posses antioxidant [1], antibacterial [2], antiviral [3] and antitumor activities [4–8]. Thienopyrimidines and their derivatives have also attracted considerable attention due to important biological properties including anticancer [9], antimicrobial [10], antiviral [11], and anti-inflammatory activities [12]. Fused thienopyrimidines with cycloalkyl substituents are potent antitumor agents [13]. These results prompted us to study the synthesis of thienopyrimidine derivatives substituted with the pyrazolo[3,4-*b*]pyridine ring system. We have previously reported several biologically active fused thienopyrimidine derivatives [14–16].

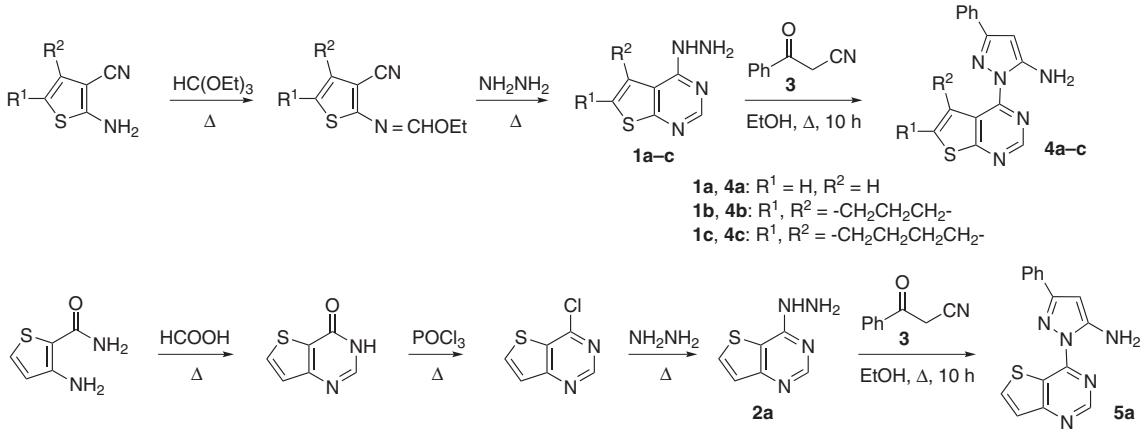
Many synthetic approaches to pyrazolo[3,4-*b*]pyridines have been developed [17]. Recently, some new pyrazolo[3,4-*b*]pyridines have been prepared by a multi-component reaction of a substituted 5-amino-1-phenyl-1*H*-pyrazole, benzoylacetonitrile and an aromatic aldehyde in the presence of a catalyst such as ammonium acetate [18], acetic acid/triethylamine [8], *L*-proline [19] or $FeCl_3$ [20]. We report here an efficient one-pot three-component synthesis of new pyrazolo[3,4-*b*]pyridine-thienopyrimidine hybrids with the concept of molecular hybridization [21] by treating 3-phenyl-1-(thienopyrimidin-4-yl)-1*H*-pyrazol-5-amine with benzoylacetonitrile and an aromatic aldehyde catalyzed by $FeCl_3$ on basic alumina.

***Corresponding author: Yang-Heon Song,** Department of Chemistry, Mokwon University, Daejeon 35349, South Korea,
e-mail: yhsong@mokwon.ac.kr
Jae Woo Park: Department of Chemistry, Mokwon University, Daejeon 35349, South Korea

Results and discussion

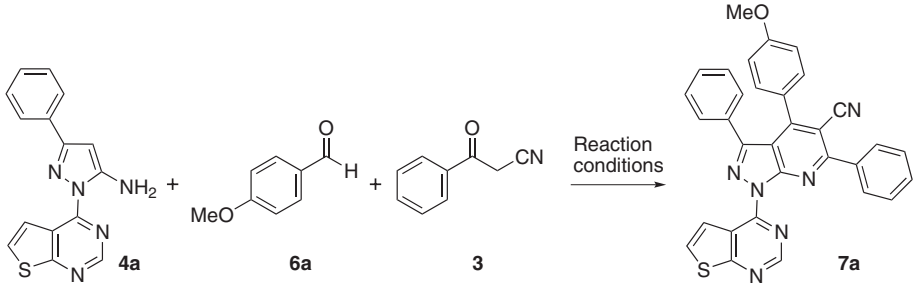
The synthesis is outlined in Scheme 1 starting from the readily available substrates **1a–c** and **2a** [22, 23]. Intermediate products **4a–c** and **5a** were easily prepared in good yields by the reaction of **1a–c** or **2a** with benzoylacetonitrile (**3**) in refluxing ethanol using the previously reported method [24]. Initially, the three-component reaction of **4a**, arylaldehyde **6a** and **3** in refluxing ethanol without catalyst or in the presence of various catalysts such as ammonium acetate, acetic acid, *L*-proline or $FeCl_3$ was investigated as a model reaction (Table 1, entries 1–5). The desired hybrid product **7a** was observed in low to moderate yields (15–61%) for the reactions conducted in refluxing ethanol. With $FeCl_3$ on basic alumina as catalyst (0.2 equiv), compound **7a** was obtained in a yield of 86% after heating for 6 h (entry 6). The use of a smaller amount of the catalyst or lowering the reaction temperature resulted in decreased yields (entries 7, 8). No further increase in yield was achieved with the use of different solvents and varying temperatures (entries 9, 10). The reaction of **4a** with **6b** and **3** under the optimized reaction conditions (using 0.2 equiv $FeCl_3$/basic Al_2O_3 in refluxing ethanol) gave a corresponding product **7b** in 82% yield (Scheme 2). The reaction of cycloalkyl-substituted **4b** or **4c** with arylaldehyde **6a–c** and **3** under the same reaction conditions afforded product **7c–f** in good yield (80–83%). When **5a** bearing a different thiophene ring was allowed to react with **6a** and **3**, the corresponding compound **8a** was obtained in 85% yield. These results show that cyclocondensation of the three components is not strongly affected by substituent on the arylaldehyde or thienopyrimidine.

All products were fully characterized by spectroscopy and elemental analysis. To definitively assign the structure of **7a–f** and **8a**, an authentic sample of **7a** was prepared by a stepwise synthesis. Thus, **4a** was first allowed to react with **3**, and the subsequent reaction of the crude product with **6a** gave **7a**. This product was identical in all respects (mp, ^{1}H NMR, and MS) with **7a** obtained from the



Scheme 1 Synthesis of reactants **4a–c** and **5a**.

Table 1 Optimization of reaction conditions for the synthesis of **7a**.[a]



Entry	Catalyst (equiv)[b]	Solvent	Time (h)	Temperature (°C)	Yield (%)[c]
1	–	EtOH	10	Reflux	32
2	NH_4OAc (0.2)	EtOH	6	Reflux	40
3	AcOH (0.2)	EtOH	6	Reflux	46
4	*L*-proline (0.2)	EtOH	6	Reflux	15
5	$FeCl_3$ (0.2)	EtOH	6	Reflux	61
6	$FeCl_3/Al_2O_3$ (0.2)	EtOH	6	Reflux	86
7	$FeCl_3/Al_2O_3$ (0.1)	EtOH	6	Reflux	65
8	$FeCl_3/Al_2O_3$ (0.2)	EtOH	10	25	44
9	$FeCl_3/Al_2O_3$ (0.2)	DMF	6	100	56
10	$FeCl_3/Al_2O_3$ (0.2)	MeCN	6	80	38

[a]Reactions were carried out with **4a** (1.0 mmol), **6a** (1.0 mmol), **3** (1.0 mmol) in an appropriate solvent (10 mL). [b]Equiv is based on $FeCl_3$. [c]Yield of isolated product.

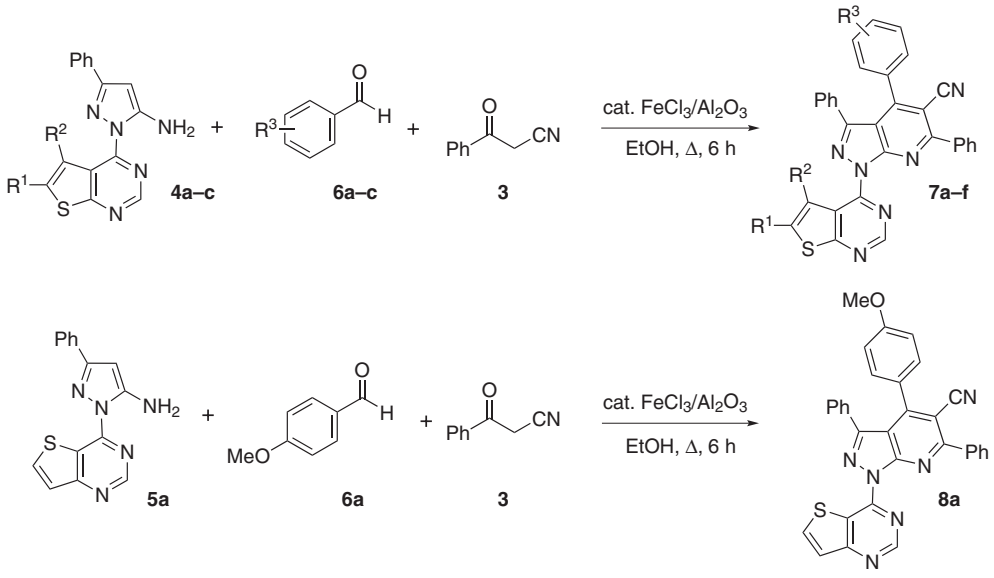
three-component reaction. This result is also consistent with the report by Jachak and co-workers [18].

Conclusions

New thienopyrimidinyl-1*H*-pyrazolo[3,4-*b*]pyridines were synthesized by the three-component reaction of 3-phenyl-1-(thienopyrimidin-4-yl)-1*H*-pyrazol-5-amine, benzoylacetonitrile and an aromatic aldehyde in refluxing ethanol in the presence of $FeCl_3$ on basic alumina. The use of the catalyst in this reaction has the advantage of enhanced yields and simple work-up compared to $FeCl_3$ alone.

Experimental

Melting points were measured by using capillary tubes on a Büchi apparatus and are uncorrected. Compounds were purified by column chromatography using Merck silica gel (70–230 mesh). The ^{1}H NMR spectra were recorded on a Unity Inova 400NB FT NMR spectrometer



4a: R^1 = H, R^2 = H
4b: R^1, R^2 = -$CH_2CH_2CH_2$-
4c: R^1, R^2 = -$CH_2CH_2CH_2CH_2$-
6a: R^3 = 4-OMe
6b: R^3 = 4-Br
6c: R^3 = 4-Me

7a: R^1 = H; R^2 = H; R^3 = 4-OMe
7b: R^1 = H; R^2 = H; R^3 = 4-Br
7c: R^1, R^2 = -$CH_2CH_2CH_2$-; R^3 = 4-OMe
7d: R^1, R^2 = -$CH_2CH_2CH_2$-; R^3 = 4-Me
7e: R^1, R^2 = -$CH_2CH_2CH_2$-; R^3 = 4-Br;
7f: R^1, R^2 = -$CH_2CH_2CH_2CH_2$-; R^3 = 4-OMe

Scheme 2 Three-component synthesis of compounds **7a–f** and **8a**.

(400 MHz) in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were recorded on a HP 59580 B spectrometer (APCI). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

Preparation of the catalyst ($FeCl_3$/basic Al_2O_3)

A mixture of hydrated ferric chloride ($FeCl_3 \cdot 6H_2O$, 4 g) and basic Al_2O_3 (20 g) in acetone (30 mL) was stirred at room temperature for 1 h and then concentrated under reduced pressure. The resulting yellow powder was dried at 100°C under reduced pressure for 2 h [25].

General procedure for the synthesis of 4a–c and 5a

A mixture of hydrazinylthienopyrimidine **1a–c** or **2** (10 mmol) and benzoylacetonitrile **3** (10 mmol) in anhydrous ethanol (20 mL) was heated under reflux for 10 h. The mixture was poured into crushed ice (20 mL) and the precipitated solid product was filtered, washed with water, and crystallized from ethanol to give pure **4a–c** or **5a**.

3-Phenyl-1-(thieno[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-5-amine (4a) Yield 75%; mp 211–212°C; ^{1}H NMR: δ 8.89 (s, 1H), 8.55 (d, 1H, *J* = 5.5 Hz), 7.97 (d, 1H, *J* = 5.5 Hz), 7.92 (m, 2H), 7.48 (m, 3H), 6.70 (s, 2H), 5.98 (s, 1H); MS: *m/z* 294.21 (M^+). Anal. Calcd for $C_{15}H_{11}N_5S$: C, 61.42; H, 3.78; N, 23.87. Found: C, 61.21; H, 3.82; N, 23.76.

1-(6,7-Dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-3-phenyl-1*H*-pyrazol-5-amine (4b) Yield 80%; mp 158–159°C; ^{1}H NMR: δ 8.81 (s, 1H), 7.83 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 6.22 (bs, 2H), 5.95 (s, 1H), 3.17 (m, 2H), 3.05 (m, 2H), 2.31 (m, 2H); MS: *m/z* 334.21 (M^+). Anal. Calcd for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.01. Found: C, 64.66; H, 4.49; N, 21.14.

3-Phenyl-1-(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-5-amine (4c) Yield 70%; mp 171–172°C; ^{1}H NMR: δ 8.94 (s, 1H), 7.78 (m, 2H), 7.42 (m, 2H), 7.39 (m, 1H), 5.94 (s, 1H), 5.85 (bs, 2H), 2.91 (m, 2H), 2.55 (m, 2H), 1.83 (m, 2H), 1.64 (m, 2H); MS: *m/z* 348.23 (M^+). Anal. Calcd for $C_{19}H_{17}N_5S$: C, 65.68; H, 4.93; N, 20.16. Found: C, 65.89; H, 4.98; N, 20.04.

3-Phenyl-1-(thieno[3,2-*d*]pyrimidin-4-yl)-1*H*-pyrazol-5-amine (5a) Yield 72%; mp 191–192°C; ^{1}H NMR: δ 8.76 (s, 1H), 8.33 (d, 1H, *J* = 5.6 Hz), 7.77 (m, 2H), 7.44 (d, 1H, *J* = 5.6 Hz), 7.30 (m, 3H), 7.20 (bs, 2H), 5.81 (s, 1H); MS: *m/z* 294.30 (M^+). Anal. Calcd for $C_{15}H_{11}N_5S$: C, 61.42; H, 3.78; N, 23.87. Found: C, 61.29; H, 3.80; N, 23.99.

General procedure for the synthesis of 7a–f and 8a

A mixture of thienopyrimidinylpyrazolamine **4a–c** or **5a** (5 mmol), arylaldehyde **6a–c** (5 mmol), benzoylacetonitrile **3** (5 mmol) and $FeCl_3$/basic Al_2O_3 (1 mmol, based on $FeCl_3$) in anhydrous ethanol (20 mL) was heated under reflux. After completion of the reaction (6 h, monitored by TLC), the mixture was diluted with ethyl acetate and the insoluble substance was filtered out. The solvent was evaporated under reduced pressure and the residue was crystallized from chloroform.

4-(4-Methoxyphenyl)-3,6-diphenyl-1-(thieno[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7a) Yield 86%; mp 255–257°C; ^{1}H NMR: δ 8.78 (s, 1H), 8.62 (d, 1H, *J* = 5.4 Hz), 7.80 (d,

1H, *J* = 5.4 Hz), 7.59 (m, 3H), 7.51 (m, 3H), 7.35 (m, 3H), 7.25 (m, 3H), 6.83 (d, 2H, *J* = 7.4 Hz), 3.76 (s, 3H); MS: *m/z* 537.16 (M^+). Anal. Calcd for $C_{32}H_{20}N_6OS$: C, 71.62; H, 3.76; N, 15.66. Found: C, 71.50; H, 3.81; N, 15.55.

4-(4-Bromophenyl)-3,6-diphenyl-1-(thieno[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7b) Yield 82%; mp 190–191°C; ^{1}H NMR: δ 8.75 (s, 1H), 8.60 (d, 1H, *J* = 5.4 Hz), 7.84 (d, 1H, *J* = 5.4 Hz), 7.68 (m, 2H), 7.50 (m, 3H), 7.40 (m, 4H), 7.28 (m, 2H), 7.19 (m, 3H); MS: *m/z* 586.01 (M^+). Anal. Calcd for $C_{31}H_{17}BrN_6S$: C, 63.59; H, 2.93; N, 14.35. Found: C, 63.74; H, 2.90; N, 14.45.

1-(6,7-Dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-4-(4-methoxyphenyl)-3,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7c) Yield: 80%; mp 237–239°C; ^{1}H NMR: δ 9.02 (s, 1H), 7.66 (m, 2H), 7.54 (m, 2H), 7.50 (m, 3H), 7.33 (m, 3H), 7.25 (m, 2H), 6.83 (m, 2H), 3.76 (s, 3H), 3.46 (m, 2H), 3.08 (m, 2H), 2.40 (m, 2H); MS: *m/z* 577.14 (M^+). Anal. Calcd for $C_{35}H_{24}N_6OS$: C, 72.90; H, 4.19; N, 14.57. Found: C, 72.77; H, 4.16; N, 14.48.

1-(6,7-Dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-3,6-diphenyl-4-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7d) Yield 83%; mp 270–271°C; ^{1}H NMR: δ 8.65 (s, 1H), 7.66 (m, 2H), 7.55 (m, 2H), 7.51 (m, 3H), 7.33 (m, 3H), 7.25 (m, 2H), 7.10 (m, 2H), 3.46 (m, 2H), 3.09 (m, 2H), 2.42 (m, 2H), 2.29 (s, 3H); MS: *m/z* 561.16 (M^+). Anal. Calcd for $C_{35}H_{24}N_6S$: C, 74.98; H, 4.31; N, 14.99. Found: C, 74.90; H, 4.27; N, 14.88.

4-(4-Bromophenyl)-1-(6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-3,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7e) Yield 81%; mp 280–281°C; ^{1}H NMR: δ 8.63 (s, 1H), 7.65 (m, 2H), 7.53 (m, 5H), 7.50 (m, 2H), 7.40 (m, 3H), 7.21 (m, 2H), 3.44 (m, 2H), 3.07 (m, 2H), 2.39 (m, 2H); MS: *m/z* 625.97 (M^+). Anal. Calcd for $C_{34}H_{21}BrN_6S$: C, 65.28; H, 3.38; N, 13.43. Found: C, 65.40; H, 3.40; N, 13.39.

4-(4-Methoxyphenyl)-3,6-diphenyl-1-(5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimi-din-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (7f) Yield 83%; mp 266–268°C; ^{1}H NMR: δ 9.08 (s, 1H), 7.93 (m, 2H), 7.50 (m, 3H), 7.27 (m, 3H), 7.15 (m, 4H), 6.77 (m, 2H), 3.81 (s, 3H), 2.92 (m, 2H), 2.32 (m, 2H), 1.87 (m, 2H), 1.68 (m, 2H); MS: *m/z* 591.19 (M^+). Anal. Calcd for $C_{36}H_{26}N_6OS$: C, 73.20; H, 4.44; N, 14.23. Found: C, 73.33; H, 4.47; N, 14.28.

4-(4-Methoxyphenyl)-3,6-diphenyl-1-(thieno[3,2-*d*]pyrimidin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (8a) Yield 85%; mp 264–265°C; ^{1}H NMR: δ 8.89 (s, 1H), 8.15 (d, 1H, *J* = 5.5 Hz), 7.72 (m, 4H), 7.60 (d, 1H, *J* = 5.5 Hz), 7.51 (m, 3H), 7.34 (m, 3H), 7.28 (m, 3H), 6.85 (d, 2H, *J* = 7.3 Hz), 3.77 (s, 3H); MS: *m/z* 537.23 (M^+). Anal. Calcd for $C_{32}H_{20}N_6OS$: C, 71.62; H, 3.76; N, 15.66. Found: C, 71.56; H, 3.73; N, 15.60.

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