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SYNTHESIS OF 2-SUBSTITUTED PYRIMIDO[5,4-*b*]INDOLIZINE DERIVATIVES FROM ACETATES OF BAYLIS-HILLMAN ADDUCTS

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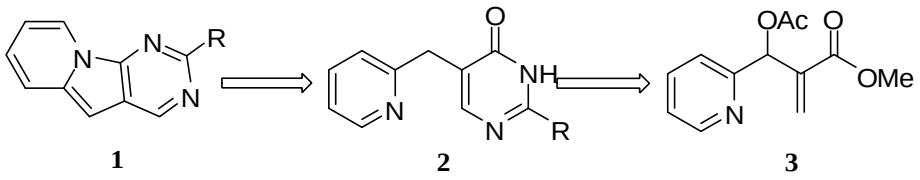
Abstract –Novel tricyclic heterocycle pyrimido[5,4-*b*]indolizine derivatives **1** were synthesized conveniently in two steps. The key intermediates 2-substituted 5-[(pyridin-2-yl)methyl]pyrimidin-4(3*H*)-ones **2** were obtained by facile cyclization of the acetate of Baylis–Hillman adduct **3** and various amidine hydrochlorides **4** in the presence of sodium ethoxide. Treatment of 5-[(pyridin-2-yl)methyl]pyrimidin-4(3*H*)-ones **2** with phosphoryl chloride by reflux afforded fused 2-substituted pyrimido[5,4-*b*]indolizines **1** in high yield.

INTRODUCTION

Indolizines are found in many natural products, mainly in their hydrogenated state.[1-3] They have received much attention in recent years due to their widely applications in biological, [4] photographic[5] and pharmaceutical use. [6-7]

Pyrimidines are an important class of compounds and have widespread applications from pharmaceuticals to materials. [8-10] In 2004, Wang et al. reported fused pyrimidines as selective inhibitors for multidrug resistance.[11] Fused pyrimidines as antiplatelet and antithrombotic drugs have also been reported.[12] Among pyrimidine derivatives we focus our interest on pyrimidine-containing tricyclic heterocycle because they served as kinase inhibitors[13] and epidermal growth factor receptor inhibitors.[14] In the course of developing novel scaffolds for medicinal application, we find that pyrimido[5,4-*b*]indolizine derivatives have not been described. Herein we report a convenient synthesis of 2-substituted pyrimido[5,4-*b*]indolizine derivatives **1** from the acetate of Baylis-Hillman adduct **3** via 5-[(pyridin-2-yl)methyl]pyrimidin-4(3*H*)-ones **2** (Scheme 1).



1 **2** **3**

Scheme 1. Retrosynthesis analysis of 2-substituted pyrimido[5,4-*b*]indolizines

RESULTS AND DISCUSSION

The starting material methyl 2-[acetoxy(pyridin-2-yl)methyl]acrylate **3** was prepared according to the procedure reported in the literature.[15] At first the reaction of benzamidine hydrochloride **4a** with the acetate **3** was investigated because **4a** is commercially available. And during the reaction a base was needed to release the free benzamidine. Several bases were tried such as sodium ethoxide, potassium carbonate, and potassium bicarbonate to neutralize the hydrochloride of **4a**, but only sodium ethoxide gave the desired cyclization product **2a**. When the ratio of base to amidine hydrochloride was 1 to 1, the best result was obtained. Further optimization of the reaction solvents revealed that the use of anhydrous THF gave superior result (Table 1).

Table 1. Optimization of Base, Solvent, and Ratio in the Synthesis of **2a** [a]

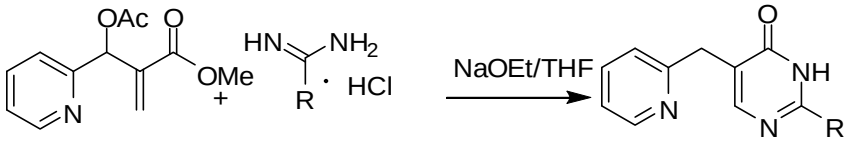
Entry	Base	Solvent	Ratio (**4a**:base)	Yield (%)
1	K_2CO_3	anhyd THF	1:1	0
		anhyd EtOH	1:1	0
2	$KHCO_3$	anhyd THF	1:1	0
		anhyd EtOH	1:1	0
3	NaOEt	anhyd THF	1:1	68[b]
		anhyd EtOH	1:1	36
		anhyd THF	1:2	0
		THF	1:1	traces

[a] all reactions were carried out at room temperature.
[b] **2a** deposited directly

According to the optimized conditions the reaction of a range of other amidine substrates with **3** were surveyed for the synthesis of 2-substituted 5-[(pyridin-2-yl)methyl]pyrimidin-4(3*H*)-ones. Substituent of amidines varied from aromatic to aliphatic and hetero groups. Most of tested aromatic benzamidine hydrochlorides which have electron-withdrawing or electron-donating groups at the meta- or para-position of amidine on the aryl ring gave good yield (Table 2, entries 2a-2e). We reckoned that not the electronic nature of the substituents but the solubility nature of the products in THF has significant effects on this reaction. When it came to aliphatic and hetero groups, **4f** and **4g** reacted with **3** at reflux to give the corresponding pyrimidinone. Purification of the crude reaction mixture by column

chromatography provided the desired **2f** and **2g** in 43% and 51% isolated yield respectively. However, when R was amino group (**4h**), the reaction was very complex and the desired product was not obtained (Table 2).

Table 2. Synthesis of 2-substituted 5-[(pyridin-2-yl)methyl]pyrimidin-4(3*H*)-ones



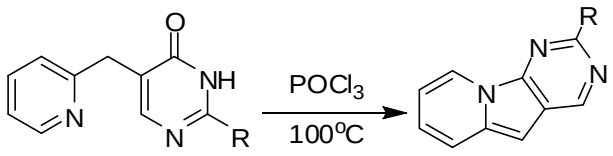
3 **4a-4h** **2a-2h**

Entry	R	Time (h)	Temp (°C)	Yield (%)
2a	Ph	12	rt	67[a]
2b	3-$MeOC_6H_4$	12	rt	60[a]
2c	4-ClC_6H_4	12	rt	68[a]
2d	4-BrC_6H_4	12	rt	44[a]
2e	4-MeC_6H_4	12	rt	30[a]
2f	Me	2	reflux	43
2g	MeS	2	reflux	51
2h	NH_2	2	reflux	0

[a] deposited directly

We next embarked on the synthesis of 2-substituted pyrimido[5,4-*b*]indolizines from **2a-2g**. Gratifyingly, all of tested pyrimidinones **2a-2g** gave the corresponding indolizines in excellent yields (Table 3, entries 1a-1g). The products **1a-1g** deposited directly in the water and they are pure enough for normal use.

Table 3. Synthesis of 2-substituted pyrimido[5,4-*b*]indolizines



2a-2g **1a-1g**

Entry	R	Time (h)	Temp(°C)	Yield (%)
1a	Ph	2	100	86
1b	3-$MeOC_6H_4$	2	100	88
1c	4-ClC_6H_4	2	100	85
1d	4-BrC_6H_4	2	100	89
1e	4-MeC_6H_4	2	100	85
1f	Me	2	100	90
1g	MeS	2	100	76

In summary, we have documented the first example of the synthesis of diverse 2-substituted pyrimido[5,4-*b*]indolizines **1a-1g**. This methodology may be applicable to other types of substrates and will contribute to the development of novel biological and pharmaceutical agents. Further studies to expand the synthetic applications of the 2-substituted pyrimido[5,4-*b*]indolizines are in progress.

EXPERIMENTAL

Melting points were measured by Büchi 510 melting point apparatus and were uncorrected. The ^{1}H NMR spectra were recorded by GEMINI spectrometer at 300 MHz and ^{13}C NMR spectra were recorded by Brucker AM-400 spectrometer at 400MHz. MS and HRMS spectra were recorded on a MAT-95 spectrometer.

Preparation of Compounds 2 (2a as example); Typical Procedure:

Benzamidine hydrochloride **4a** (1 g, 6.4mmol) was added into a solution of sodium hydride(60% in mineral oil, 256 mg, 6.4 mmol) in anhydrous EtOH (20 mL) under an atmosphere of nitrogen at rt. The mixture was stirred for 1 h, then filtered. The filtrate was concentrated in vacuo and the solvent was changed to anhydrous THF (30 mL). **3** (1g, 4.3 mmol) was added and stirred at rt for 12 h. The precipitate was isolated by filtration giving crude **2a** 1.1 g. The crude product was purified by crystallization from EtOH to give the pure products **2a** (600 mg, 67%).

Preparation of Compounds 1 (1a as example); Typical Procedure:

Compound **2a** (600 mg, 2.3 mmol) in phosphoryl chloride (5 mL) was heated at 100 °C for 2 h. The reaction mixture was poured slowly into ice water (50 mL) and the pH was adjusted to about 7-8 with $NaHCO_3$. After standing at rt for 1 h, the resulting precipitated solid was collected by filtration and washed with H_2O, providing the desired products **1a** in 86% yield.

Spectral data for products:

2-Phenyl-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2a)

White solid, mp 220-221 °C; ^{1}H NMR (300 MHz, CDCl3) δ 4.04 (s, 2H), 7.10-7.14 (m, 1H), 7.32-7.35 (d, *J* =9 Hz, 1H), 7.45-7.58 (m, 4H), 8.12-8.17 (m, 3H), 8.52-8.54 (m, 1H). MS (EI) *m/z* (%): 263 (M^+, 100), 144 (20), 117 (18). HRMS (EI) calcd. for $C_{16}H_{13}N_3O$, 263.1059; found 263.1055.

2-(3-Methoxyphenyl)-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2b)

White solid, mp 188-190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.04 (s, 2H), 7.07-7.14 (m, 2H), 7.33-7.41 (m, 2H), 7.52-7.58 (td, *J* = 7.5, 1.5 Hz, 1H), 7.69-7.72 (m, 2H), 8.09 (s, 1H), 8.52-8.54 (m, 1H). MS (EI) *m/z* (%): 293 (M^+, 100), 149 (50), 79 (18). HRMS (EI) calcd. for $C_{17}H_{15}N_3O_2$, 293.1164; found

293.1172.

2-(4-Chlorophenyl)-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2c)

White solid, mp 250-252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (s, 2H), 7.19-7.23 (m, 1H), 7.30-7.32 (d, *J* = 7.8Hz, 1H), 7.56-7.61 (m, 2H), 7.67-7.73 (td, *J* = 7.8, 1.8Hz, 1H), 7.99 (s, 1H), 8.09-8.12 (d, *J* = 9Hz, 2H), 8.44-8.47 (m,1H). MS (EI) *m/z* (%): 297 (M^+, 100), 280 (5). HRMS(EI) calcd. for $C_{16}H_{12}ClN_3O$, 297.0669; found 297.0665.

2-(4-Bromophenyl)-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2d)

White solid, mp 240-242 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 2H), 7.17-7.21 (m, 1H), 7.28-7.31 (d, *J* = 8.1Hz, 1H), 7.65-7.71 (m, 2H), 7.81-7.84 (m, 1H), 7.94 (s, 1H), 8.02-8.05 (d, *J* = 8.4Hz, 2H), 8.42-8.46 (m,1H), 10.8 (s, br,1H). MS (EI) *m/z* (%): 341 (M^+, 100). HRMS (EI) calcd. for $C_{16}H_{12}BrN_3O$, 341.0164; found 341.0176.

5-(Pyridin-2-ylmethyl)-2-*p*-tolylpyrimidin-4(3*H*)-one (2e)

White solid, mp 218-220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42(s, 3H), 4.04 (s, 2H), 7.09-7.13 (dd, *J* = 7.2, 4.8Hz, 1H), 7.25-7.34 (m, 3H), 7.52-7.57 (td, *J* = 7.8, 1.8 Hz, 1H), 8.02-8.05 (d, *J* = 8.4, 2H), 8.06 (s, 1H), 8.52-8.55 (m, 1H), 12.50 (s, br,1H). MS (EI) *m/z* (%): 277 (M^+, 20), 134 (80). HRMS (EI) calcd. for $C_{17}H_{15}N_3O$, 277.1215; found 277.1212.

2-Methyl-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2f)

White solid, mp 117-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38(s, 3H), 3.95 (s, 2H), 7.10-7.12 (m, 1H), 7.29-7.32 (d, *J* = 7.5, 1H), 7.56-7.62 (td, *J* = 7.5, 1.8 Hz, 1H), 7.90 (s, 1H), 8.51-8.52 (m, 1H), 13.09 (s, br,1H). MS (EI) *m/z* (%): 201 (M^+, 50), 77 (20). HRMS (EI) calcd. for $C_{11}H_{11}N_3O$, 201.0902; found 201.0907.

2-(Methylthio)-5-(pyridin-2-ylmethyl)pyrimidin-4(3*H*)-one (2g)

White solid, mp 138-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52(s, 3H), 3.94 (s, 2H), 7.10-7.14 (m, 1H), 7.34-7.37 (d, *J* = 7.5, 1H), 7.57-7.63 (td, *J* = 7.5, 1.5 Hz, 1H), 7.82 (s, 1H), 8.50-8.53 (m, 1H); MS (EI) *m/z* (%): 233 (M^+, 100), 186 (40), 78 (10). HRMS (EI) calcd. for $C_{11}H_{11}N_3OS$, 233.0623; found 233.0632.

2-Phenylpyrimido[5,4-*b*]indolizine (1a)

Yellow solid, mp 116-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57-6.61 (m, 2H), 6.96-7.01 (m, 1H), 7.45-7.58 (m, 4H), 8.59-8.63 (m, 2H), 8.76-8.79 (d, *J* = 6.9, 1H), 9.33 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 88.31, 109.46, 117.48, 119.84, 123.77, 124.92, 127.82, 128.55, 129.52, 137.02, 138.62, 144.72,

150.41, 154.98. MS (EI) *m/z* (%): 245 (M^+, 100), 142 (70). HRMS (EI) calcd. for $C_{16}H_{13}N_3$, 245.0953; found 245.0960.

2-(3-Methoxyphenyl)pyrimido[5,4-*b*]indolizine (1b)

Yellow solid, mp 131-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.60-6.64 (m, 2H), 6.99-7.04 (m, 2H), 7.41-7.46 (m, 2H), 8.18-8.24 (m, 2H), 8.78-8.81 (m, 1H), 9.34 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 55.45, 88.47, 109.60, 112.62, 116.05, 117.53, 119.87, 120.44, 123.82, 125.068, 129.56, 137.27, 150.09, 154.60, 160.03. MS (EI) *m/z* (%): 275 (M^+, 100), 142 (90). HRMS (EI) calcd. for $C_{17}H_{13}N_3O$, 275.1059; found 275.1056.

2-(4-Chlorophenyl)pyrimido[5,4-*b*]indolizine (1c)

Yellow solid, mp 156-158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61-6.66 (m, 2H), 7.01-7.06 (m, 1H), 7.43-7.50 (m, 3H), 8.53-8.58 (m, 2H), 8.75-8.78 (m, 1H), 9.33 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 88.46, 109.65, 117.56, 119.88, 123.73, 125.11, 128.71, 129.09, 135.58, 137.07, 137.23, 144.59, 150.32, 153.84. MS (EI) *m/z* (%): 279 (M^+, 100), 142 (60). HRMS (EI) calcd. for $C_{16}H_{10}ClN_3$, 279.0563; found 279.0563.

2-(4-Bromophenyl)pyrimido[5,4-*b*]indolizine (1d)

Yellow solid, mp 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86-6.92 (m, 2H), 7.23-7.26 (m, 1H), 7.58-7.61 (m, 1H), 7.73-7.76 (m, 2H), 8.56-8.58 (m, 2H), 8.82-8.84 (dd, *J* = 7.2, 1.2 Hz, 1H) 9.629 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 89.15, 110.13, 117.34, 119.95, 123.81, 124.47, 125.52, 129.46, 131.77, 136.45, 137.77, 144.49, 149.98, 152.99. MS (EI) *m/z* (%): 323 (M^+, 100), 142 (100). HRMS (EI) calcd. for $C_{16}H_{10}BrN_3$, 323.0058; found 323.0049.

2-*p*-Tolylpyrimido[5,4-*b*]indolizine (1e)

Yellow solid, mp 130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.67-6.71 (m, 2H), 7.05-7.10 (dd, *J* = 9, 6.3 Hz, 1H), 7.34-7.37 (d, *J* = 8.1Hz, 1H), 7.46-7.49 (d, *J* = 9.6Hz, 1H), 8.53-8.56 (d, *J* = 8.1 Hz, 2H), 8.76-8.79 (dd, *J* = 7.5, 0.9 Hz, 1H) 9.43 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.44, 88.32, 109.41, 117.25, 119.81, 123.73, 124.81, 127.74, 129.32, 135.75, 136.91, 139.66, 144.71, 150.22, 155.03. MS (EI) *m/z* (%): 259 (M^+, 100), 142 (100). HRMS (EI) calcd. for $C_{17}H_{13}N_3$, 259.1109; found 259.1110.

2-Methylpyrimido[5,4-*b*]indolizine (1f)

Yellow solid, mp 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 3H), 6.53-6.58 (m, 2H), 6.92-6.98 (m, 1H), 7.38-7.42 (td, *J* = 9.3, 0.9Hz, 1H), 8.62-8.65 (m, 1H), 9.18 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.86, 87.87, 109.29, 116.59, 119.78, 123.42, 124.38, 136.09, 144.49, 150.35, 157.86. MS (EI) *m/z* (%): 183 (M^+, 100), 142 (90). HRMS (EI) calcd. for $C_{11}H_9N_3$, 183.0796; found 183.0793.

2-(Methylthio)pyrimido[5,4-*b*]indolizine (1g)

Yellow solid, mp 100-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3H), 6.49-6.55 (m, 2H), 6.88-6.93 (m, 1H), 7.34-7.38 (dd, *J* = 9.3, 1.2Hz, 1H), 8.53-8.56 (m, 1H), 9.06 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.41, 88.17, 109.46, 115.66, 119.81, 123.15, 123.97, 135.38, 144.69, 150.81, 161.41. MS (EI) *m/z* (%): 215 (M^+, 80), 182 (100), 142 (60). HRMS (EI) calcd. for $C_{11}H_9N_3S$, 215.0517; found 215.0527.

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