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An Efficient One-Step Synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines in Basic Ionic Liquid [bmim]OH

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Abstract: Chain 1,3-dicarbonyl compounds were firstly used as starting material to react with 5-amino-3-methyl-1-phenylpyrazol and aromatic aldehydes to prepare 1*H*-pyrazolo[3,4-*b*]pyridines in basic ionic liquid [bmim]OH. The one-step three-component reaction is simple and efficient. Additionally, water was the only one by-product during the whole process.

Keywords: Basic ionic liquid, pyrazolo[3,4-b]pyridines.

1. INTRODUCTION

Pyrazolopyridine is an important fused heterocyclic framework which has attracted significant attention because of their biological activities for many years. They were used as dopamine D3 receptor antagonist, [1] partial agonist, [1] dopamine D4 antagonist, [2] adenosine A1 receptor antagonist, [3] TYK2 kinase and PDE10a inhibitors [4, 5]. Particularly, pyrazolo[3,4-*b*]pyridines are useful for the treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhaged stress, drug and alcohol withdrawal symptoms, drug addiction and infertility [6]. Recently, pyrazolopyridines were used as inhibitors of the kinase LRRK2 to treat cancer and neurodegenerative diseases [7]. Therefore, their synthesis is very important in medicine and pharmaceutics chemistry.

By far, there have been many approaches to synthesize pyrazoles. In 1986, Nielsen [8] firstly obtained pyrazolo[3,4-*b*]quinolines from aminopyrazole, cyclohexanone and aromatic amine with P_4O_{10} as catalyst. Then, pyrazolo[3,4-*b*]quinolines were prepared by several groups in succession [8-10]. But most of them are associated with one or more of the following drawbacks: unavailable raw material, lower yields, higher temperatures, rigorous reaction conditions and use of organic solvent.

Most of all, due to their lower reactivity than that of ring 1,3-dicarbonyl compounds, chain 1,3-dicarbonyl compounds haven't been employed as substrate until now to synthesize pyrazolo[3,4-*b*]pyridines.

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Herein, we report a new method to access pyrazolo[3,4-*b*]pyridines *via* an efficient one-step three-component reaction of chain 1,3-dicarbonyl compounds, 5-amino-3-methyl-1-phenylpyrazol and aromatic aldehydes in basic ionic liquid [bmim]OH. Moreover, basic ionic liquids are rarely used as solvent in organic reactions, so, we hope our efforts can provide some support to the synthesis of pyrazolopyridines and give some supplements for the applied range of basic ionic liquids (Scheme **1**).

2. RESULTS AND DISCUSSION

Initially, the three-component reaction of *p*-fluorobenzaldehyde (**1a**), 5-amino-3-methyl-1-phenylpyrazol (**2**) and acetylacetone **(3**) was investigated to optimize the reaction conditions. The results are summarized in Table **1**. As can be seen, when water was chosen as solvent, the yield was 58% (Entry **1**). But when DMF (Entry **2**) and DMSO (Entry **3**) was taken as medium, there is no desired product. Then, ethanol, [bpy]Br, [bpy]BF_4, [bmim]Br and [bmim]BF_4 (Entries **4**-**8**) was tested. It was found that the solvent with higher *p*Ka could give the higher yield, which indicated that this reaction is a nucleophilic one. So, basic ionic liquid [bmim]OH (*p*H=9~10) was used to increased the yield (91%, Entry **9**). Subsequently, we found the optimum temperature is 60 ^oC (Entries **10**-**12**). Finally, the reaction time was investigated. The results shown in Table **1** indicated that the optimum condition is to react in [bmim]OH under 60 ^oC for 6 h.

Under the optimal conditions, the reaction of a variety of aromatic aldehydes with acetylacetone and 5-amino-3-methyl-1-phenylpyrazol was investigated (Table **2**). The Product **5** (except 5j), was obtained with the yields ranging from 78 to 89 %. We think the reason is the activity of acety-

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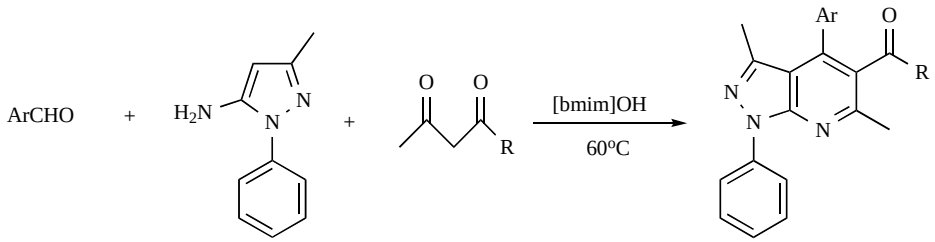
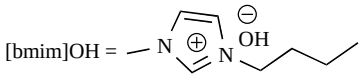


1 **2** **3 (R=CH_3)** **4 (R=OC_2H_5)** **5 (R=CH_3)** **6 (R=OC_2H_5)**

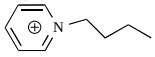


Scheme 1. One-pot synthesis of pyrazolo[3,4-*b*]pyridines.

Table 1. Optimization of Reaction Conditions.

Entry	Solvent	T(°C)	Time (h)	Yield (%)
1	H_2O	60	6	58
2	DMF	60	6	NP[a]
3	DMSO	60	6	NP
4	EtOH (95%)	60	6	53
5	[bpy] Br[b]	60	6	NP
6	[bpy]BF_4	60	6	35
7	[bmim]Br	60	6	NP
8	[bmim]BF_4	60	6	46
9	[bmim]OH	60	6	91
10	[bmim]OH	25	6	NP
11	[bmim]OH	40	6	46
12	[bmim]OH	80	6	90
13	[bmim]OH	60	2	43
14	[bmim]OH	60	4	69
15	[bmim]OH	60	8	92
16	[bmim]OH	60	10	90

[a]: No desired products;

[b]: [bpy] is  .

lacetone is too low to react with 3,4,5-trimethoxybenzaldehyde (1j) which has high steric hindrance and low reactivity. The results indicated that the electronic nature of substituted group has no obvious influence on the yield. Subsequently, another chain 1,3-dicarbonyl compound ethyl acetoacetate (4) was used as reagent to react with aromatic aldehydes (1) and **5-amino-3-methyl-1-phenylpyrazol** (**2**), the yields of **6** displayed a similar regulation with that of **5**.

In summary, low active chain 1,3-dicarbonyl compounds were applied to synthesize 1*H*-pyrazolo[3,4-*b*]pyridines in basic ionic liquid [bmim]OH simply and efficiently. Besides the advantages that all the reactants were added at the beginning and the same reaction conditions were maintained throughout, the features of this process include: (1) commercial available starting material; (2) mild reaction conditions; (3) good yields; (4) convenient procedure; (5) water was the only one by-product.

3. EXPERIMENTAL

General Information

All reagents were purchased from commercial sources and used without purification. TLC analysis was performed

Table 2. Synthesis of Compounds 5 and 6 in Ionic Liquid [bmim]OH.

Entry	Ar	Product	Time (h)	Yield (%)	mp (°C)
1	4-FC_6H_4	**5a**	6	84	167-168
		6a		82	213-214
2	4-ClC_6H_4	**5b**	6	83	144-146
		6b		83	237-238
3	4-BrC_6H_4	**5c**	7	79	147-149
		6c		85	209-210
4	2,4-$Cl_2C_6H_3$	**5d**	7	81	113-114
		6d		83	122-123
5	4-CNC_6H_4	**5e**	7	78	192-193
		6e		73	136-138
6	3-$NO_2C_6H_4$	**5f**	12	80	149-150
		6f		65	137-138
7	4-MeC_6H_4	**5g**	6	85	250-251
		6g		81	123-124
8	4-$MeOC_6H_4$	**5h**	6	87	161-162
		6h		88	218-219
9	2,3-$(MeO)_2C_6H_3$	**5i**	6	88	133-135
		6i		86	214-215
10	3,4,5-$(MeO)_3C_6H_2$	**5j**	6	-	-
		6j		83	116-118

with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in DMSO-d_6 or $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbances are reported in cm^{-1}.

General Procedure for the Preparation of 1*H*-pyrazolo[3,4-*b*]pyridines

Aromatic aldehyde (**1**, 2 mmol), 5-amino-3-methyl-1-phenylpyrazol (**2**, 2 mmol), acetylacetone (**3**, 2 mmol), and [bmim]OH (2 mL) were added into a one-necked 50 mL round bottom flask, the mixture was then heated in a 60 °C oil bath. When the reaction was finished (monitored by TLC), distilled water was poured into, the deposition was then filtered and recrystallized with DMF to give **5**.

With the same procedure, ethyl acetoacetate (**4**, 2 mmol) was allowed to take place of acetylacetone to give product **6**.

1-(4-(4-methoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5h).

Yellow crystal (DMF), mp 161.2-161.6 °C; ^{1}H NMR (400MHz, $CDCl_3$): 1.98 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.07 (d, J = 8.4 Hz, 2H, ArH), 7.29-7.31 (m, 3H, ArH), 7.52 (t, J = 8.4 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 23.6, 32.2, 59.9, 114.1, 120.3, 121.7, 124.0, 125.6, 128.2, 129.1, 131.8, 138.9, 143.0, 145.5, 148.9, 152.2, 154.1, 204.3. HR-MS: cacld for $C_{23}H_{21}N_3O_2$ $(M+H)^+$ 372.1707, found 372.1704.

1-(4-(4-fluorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pridine-5-yl)ethanone (5a).

Yellow crystal (DMF), mp 167-168 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.06 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.23(t, 2H, J=8.0 Hz, ArH), 7.32(t, 1H, J=7.2 Hz, ArH), 7.37-7.40(m, 2H, ArH), 7.54(t, 2H, J=8.0 Hz, ArH), 8.30(d, 2H, J=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 14.4, 23.4, 32.3, 112.4, 115.3, 115.6, 120.4, 125.7, 129.1, 131.4, 131.5, 131.7, 138.8, 140.6, 142.8, 149.2, 153.9, 204.9. HR-MS: cacld for $C_{22}H_{18}FN_3O$ $(M+Na)^+$ 382.1326, found 382.1293.

1-(4-(4-chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pridine-5-yl)ethanone (5b).

Yellow crystal (DMF), mp 144-146 °C; ^{1}H NMR (400MHz, DMSO): δ 2.02 (s, 3H, CH_3), 2.11 (s, 3H, CH_3),

2.60 (s, 3H, CH_3), 7.35 (t, 1H, *J*=7.6 Hz, ArH), 7.48(d, 2H, *J*=8.4 Hz, ArH), 7.58(t, 2H, *J*=7.6 Hz, ArH), 7.64 (d, 2H, *J*=8.0 Hz, ArH), 8.24 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR (100MHz, DMSO): δ14.4, 23.4, 32.5, 112.2, 120.5, 125.8, 128.6, 129.2, 131.1, 133.1, 134.2, 138.8, 140.4, 142.8, 154.0, 173.1, 211.1. HR-MS: cacld for $C_{22}H_{18}ClN_3O$ $(M+Na)^+$ 398.1030, found 398.1007.

1-(4-(4-bromophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5c).

Yellow crystal (DMF), mp 147-149 °C; ^{1}H NMR (400MHz, DMSO): δ 2.02 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.35 (t, 1H, *J*=7.6 Hz, ArH), 7.41(d, 2H, *J*=8.0 Hz, ArH), 7.57(t, 2H, *J*=8.4 Hz, ArH), 7.77 (d, 2H, *J*=8.4 Hz, ArH), 8.24 (d, 2H, *J*=7.6 Hz, ArH). ^{13}C NMR (100MHz, DMSO): δ 14.5, 23.4, 32.5, 112.7, 120.5, 122.8, 125.8, 129.2, 131.3, 131.4, 131.6, 133.4, 139.0, 140.4, 142.8, 154.0, 183.4, 204.8. HR-MS: cacld for $C_{22}H_{18}BrN_3O$ $(M+Na)^+$ 442.0531, found 442.0555.

1-(4-(2,4-dichlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5d).

Yellow crystal (DMF), mp 113-114 °C; ^{1}H NMR (400MHz, DMSO): δ 1.97 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.65(s, 3H, CH_3), 7.36 (t, 1H, *J*=7.6 Hz, ArH), 7.58(t, 2H, *J*=8.0 Hz, ArH), 7.64(d, 1H, *J*=2.4 Hz, ArH), 7.70(dd, 1H, *J*=8.4 Hz, ArH), 7.76 (d, 1H, *J*=8.8 Hz, ArH), 8.24 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, DMSO): δ 13.0, 23.6, 32.0, 112.7, 116.1, 118.7, 120.5, 125.9, 129.2, 130.7, 131.0, 131.1, 132.0, 137.0, 138.7, 142.5, 149.1, 151.4, 154.7, 214.5. HR-MS: cacld for $C_{22}H_{17}Cl_2N_3O$ $(M+H)^+$ 410.0821, found 410.0790.

4-(5-acetyl-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-yl)benzonitrile (5e).

Yellow crystal (DMF), mp 192-193 °C; ^{1}H NMR (400MHz, DMSO): δ 1.97 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.35 (t, 1H, *J*=7.6 Hz, ArH), 7.58(t, 2H, *J*=7.6 Hz, ArH), 7.68(d, 2H, *J*=8.0 Hz, ArH), 8.05 (d, 2H, *J*=8.0 Hz, ArH), 8.24 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR (100MHz, DMSO): δ 14.4, 23.5, 32.6, 103.4, 112.1, 118.4, 120.6, 125.9, 129.2, 130.3, 131.4, 132.3, 138.8, 139.1, 139.9, 142.7, 149.2, 154.1, 204.6. HR-MS: cacld for $C_{23}H_{18}N_4O$ $(M+H)^+$ 367.1553, found 367.1533.

1-(3,6-dimethyl-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5f).

Yellow crystal (DMF), mp 149-150 °C; ^{1}H NMR (400MHz, DMSO): δ 1.98 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 7.06-7.54 (m, 5H, ArH), 7.58 (t, 1H, *J*=8.0 Hz, ArH), 7.87 (d, 1H, *J*=7.6 Hz, ArH), 8.17 (d, 1H, *J*=8.0 Hz, ArH), 8.42 (s, 1H, ArH). ^{13}C NMR (100MHz, DMSO): δ 14.5, 23.4, 32.2, 113.8, 120.4, 125.7, 126.1, 127.1, 129.1, 130.6, 138.9, 141.7, 142.9, 149.3, 153.9, 158.7, 159.8, 174.9, 205.2. HR-MS: cacld for $C_{22}H_{18}N_4O_3$ $(M+H)^+$ 387.1452, found 387.1476.

1-(3,6-dimethyl-1-phenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5g).

Yellow crystal (DMF), mp 250-251 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.03 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 7.05 (d, 2H, *J*=8.4 Hz, ArH), 7.32 (d, 3H, *J*=8.4 Hz, ArH), 7.54 (t, 2H, *J*=8.0 Hz, ArH), 8.30 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 14.4, 23.4, 32.3, 112.4, 115.3, 115.6, 120.4, 125.7, 129.1, 131.4, 131.5, 131.7, 138.8, 142.8, 149.2, 153.9, 204.9. HR-MS: cacld for $C_{23}H_{21}N_3O$ $(M+Na)^+$ 378.1577, found 378.1561.

1-(4-(2,3-dimethoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)ethanone (5i).

Yellow crystal (DMF), mp 133-135 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.81 (d, 1H, *J*=7.6 Hz, ArH), 7.07(d, 1H, *J*=8.0 Hz, ArH), 7.16(t, 1H, *J*=8.0 Hz, ArH), 7.31(d, 1H, *J*=7.2 Hz, ArH), 7.53 (t, 2H, *J*=7.6 Hz, ArH), 8.32 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 13.2, 23.6, 32.2, 55.8, 59.9, 112.9, 114.1, 120.3, 121.7, 124.0, 125.6, 128.1, 129.1, 131.8, 138.4, 138.9, 143.0, 145.5, 148.9, 152.2, 154.1. HR-MS: cacld for $C_{24}H_{23}N_3O_3$ $(M+Na)^+$ 424.1632, found 424.1641.

Ethyl-4-(4-fluorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pridine-5-carboxylate (6a).

White powder (DMF), mp 213-214 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.02 (t, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 4.21 (q, 2H, CH_2), 7.30 (t, 3H, *J*=8.0 Hz, ArH), 7.46-7.57 (m, 4H, ArH), 8.42 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 14.7, 15.0, 15.3, 62.5, 113.6, 115.3, 115.5, 120.3, 121.1, 125.2, 129.0, 130.2, 130.6, 130.7, 139.6, 140.2, 144.2, 150.5, 207.0. HR-MS: cacld for $C_{23}H_{20}FN_3O_2$ $(M+H)^+$ 390.1612, found 390.1611.

Ethyl-4-(4-chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6b).

Yellow crystal (DMF), mp 237-238 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.26 (t, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.21 (q, 2H, CH_2), 7.28-7.32 (m, 2H, ArH), 7.43 (d, 1H, *J*=7.6 Hz, ArH), 7.51 (d, 2H, *J*=8.0 Hz, ArH), 7.53 (d, 2H, *J*=8.0 Hz, ArH), 8.39 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 14.4, 23.4, 32.5, 69.0, 112.2, 120.5, 125.8, 128.6, 129.2, 131.1, 133.1, 134.2, 138.8, 140.4, 142.8, 154.0, 173.1. HR-MS: cacld for $C_{23}H_{20}ClN_3O_2$ $(M+H)^+$ 406.1317, found 406.1316.

Ethyl-4-(4-bromophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6c).

Yellow crystal (DMF), mp 209-210 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.02 (t, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 4.09 (q, 2H, CH_2), 7.30 (t, 2H, *J*=7.6 Hz, ArH), 7.37 (d, 1H, *J*=8.0 Hz, ArH), 7.55 (t, 2H, *J*=7.6 Hz, ArH), 7.72 (d, 2H, *J*=8.0 Hz, ArH), 8.39 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 14.3, 23.5, 32.6, 34.5, 112.4, 120.5, 125.6, 128.2, 129.2, 130.2, 131.3, 132.3, 138.0,

139.1, 139.8, 142.6, 154.0, 204.6. HR-MS: cacld for $C_{23}H_{20}BrN_3O_2$ $(M+H)^+$ 450.0812, found 450.0811.

Ethyl-4-(2,4-dichlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6d).

Yellow crystal (DMF), mp 123 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.01 (t, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.12 (q, 2H, CH_2), 6.71 (d, 1H, *J*=8.0 Hz, ArH), 6.93 (d, 1H, *J*=8.8 Hz, ArH), 7.30 (t, 2H, *J*=8.0 Hz, ArH), 7.42-7.54 (m, 2H, ArH), 8.27 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 13.5, 24.4, 61.3, 112.7, 121.1, 122.5, 125.9, 129.0, 130.0, 130.4, 131.7, 132.5, 136.4, 139.1, 140.0, 143.1, 149.9, 157.2, 167.5, 206.9. HR-MS: cacld for $C_{23}H_{19}Cl_2N_3O_2$ $(M+H)^+$ 440.0927, found 440.0935.

Ethyl-4-(4-cyanophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6e).

Yellow crystal (DMF), mp 136-138 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.35 (t, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 7.31 (t, 2H, *J*=7.2 Hz, ArH), 7.55(t, 3H, *J*=8.0Hz, ArH), 7.67(d, 1H, *J*=8.0 Hz, ArH), 7.90 (d, 1H, *J*=8.0 Hz, ArH), 8.38 (d, 2H, *J*=7.6 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 15.0, 15.6, 30.9, 112.8, 113.2, 113.3, 120.3, 125.4, 129.0, 129.8, 131.9, 138.4, 139.3, 139.4, 143.6, 150.3, 207.0. HR-MS: cacld for $C_{24}H_{20}N_4O_2$ $(M+H)^+$ 397.1659, found 397.1673.

Ethyl-3,6-dimethyl-4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6f).

Yellow powder (DMF), mp 137-138 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.04 (t, 3H, *J*=7.2 Hz, CH_3), 2.07 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.11 (q, 2H, CH_2), 7.34 (t, 1H, *J*=7.6 Hz, ArH), 7.55 (t, 2H, *J*=7.6 Hz, ArH), 7.70-7.77 (m, 2H, ArH), 8.29 (d, 2H, *J*=8.0 Hz, ArH), 8.33 (s, 1H, ArH), 8.39 (d, 1H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 13.7, 15.1, 113.2, 113.3, 120.3, 123.5, 125.2, 129.0, 129.1, 130.5, 131.4, 133.2, 139.5, 144.1, 150.4, 207.0. HR-MS: cacld for $C_{23}H_{20}N_4O_4$ $(M+H)^+$ 417.1557, found 417.1557.

Ethyl-3,6-dimethyl-1-phenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6g).

Yellow crystal (DMF), mp 123-124 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 0.98 (t, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 4.07 (q, 2H, CH_2), 7.30 (d, 2H, *J*=8.0 Hz, ArH), 7.24 (m, 2H, ArH), 7.51 (t, 3H, *J*=8.0 Hz, ArH), 8.26 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 13.7, 14.7, 21.4, 23.9, 61.2, 113.1, 121.1, 123.9, 125.6, 128.6, 128.7, 129.0, 132.4, 138.5, 139.4, 143.5, 144.2, 150.0, 155.7, 168.8. HR-MS: cacld for $C_{24}H_{23}N_3O_2$ $(M+H)^+$ 386.1863, found 386.1889.

Ethyl-4-(4-methoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6h).

Yellow powder (DMF), mp 218-219 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.29 (t, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.30 (q, 2H, CH_2), 7.08 (d, 2H, *J*=8.4 Hz, ArH), 7.29 (d, 1H, *J*=7.6 Hz, ArH), 7.38 (d, 1H, *J*=8.0 Hz, ArH), 7.54 (t, 3H, *J*=7.6 Hz, ArH), 8.41 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 13.0, 23.6, 32.0, 112.0, 120.5, 125.9, 129.2, 130.6, 131.0, 131.1, 131.2, 132.0, 134.8, 137.0, 138.7, 142.5, 149.0, 154.6, 203.7. HR-MS: cacld for $C_{24}H_{23}N_3O_3$ $(M+H)^+$ 402.1812, found 402.1812.

Ethyl-4-(2,3-dimethoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6i).

White powder (DMF), mp 214-215 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.96(s, 3H, OCH_3), 4.22 (q, 2H, CH_2), 6.71 (d, 1H, *J*=8.0 Hz, ArH), 6.93 (d, 1H, *J*=8.8 Hz, ArH), 7.05-7.21 (m, 2H, ArH), 7.31 (d, 1H, *J*=8.4 Hz, ArH), 7.51 (t, 2H, *J*=7.6 Hz, ArH), 8.25 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ 12.3, 13.5, 14.1, 55.8, 61.1, 96.3, 112.6, 112.8, 115.7, 118.7, 120.1, 121.2, 124.0, 124.3, 128.94, 129.0, 129.1, 145.8, 207.0. HR-MS: cacld for $C_{25}H_{25}N_3O_4$ $(M+H)^+$ 432.1918, found 432.1917.

Ethyl-3,6-dimethyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (6j).

Yellow crystal (DMF), mp 116-118 °C; ^{1}H NMR (400MHz, DMSO): δ 1.02 (t, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.86 (s, 6H, OCH_3), 3.93(s, 3H, OCH_3), 4.10 (q, 2H, CH_2), 6.60 (s, 2H, ArH), 7.52 (t, 3H, *J*=8.0 Hz, ArH), 8.26 (d, 2H, *J*=8.0 Hz, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ13.8, 14.8, 23.8, 56.2, 61.1, 61.4, 106.2, 112.8, 113.2, 121.1, 123.7, 125.8, 129.0, 130.8, 138.2, 139.3, 143.3, 143.7, 152.9, 155.8, 168.8. HR-MS: cacld for $C_{26}H_{27}N_3O_5$ $(M+H)^+$ 462.2023, found 462.2044.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. Interactive SAR studies: rational discovery of super-potent and highly selective dopamine D3 receptor antagonists and partial agonists. *J. Med. Chem.*, **2002**, *45(21)*, 4594-4597.

[2] Löber, S.; Hübner, H.; Utz, W.; Gmeiner, P. Rationally based efficacy tuning of selective dopamine D4 receptor ligands leading to the complete antagonist 2-[4-(4-Chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-a]pyridine (FAUC 213). *J. Med. Chem.*, **2001**, *44(17)*, 2691-2694.

[3] Kuroda, S.; Akahane, A.; Itani, H.; Nishimura, S.; Durkin, K.; Tenda, Y.; Sakane, K. Novel adenosine A1 receptor antagonists. Synthesis and structure-activity relationships of a novel series of 3-(2-cyclohexenyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-

phenylpyrazolo[1,5-a]pyridines. *Bioorg. Med. Chem.*, **2000**, *8(1)*, 55-64.

[4] Blench, T.; Goodacre, S.; Lai, Y. J.; Liang, Y.; MacLeod, C.; Magnuson, S.; Tsui, V.; Williams, K.; Zhang, B. R. Preparation of pyrazolopyridines and their use as TYK2 kinase inhibitors. Internation Patent WO 2012066061, May 24, **2012**.

[5] Davenport, T.; Vile, J.; Pal, S. Pyrazolopyridine compounds as PDE10a inhibitors. Internation Patent WO 2012019954, Feb 16, **2012**.

[6] Chen, Y. L. Pyrazolo- and pyrrolopyridines useful as CRF antagonists. Internation Patent WO 9534563, Dec 21, **1995**.

[7] Chan, B.; Chen, H. F.; Estrada, A.; Shore, D.; Sweeney, Z.; McIver, E. Pyrazolopyridines as inhibitors of the kinase LRRK2 and their preparation and use in the treatment of cancer and neurodegenerative diseases. Internation Patent WO 2012038743, Mar 29, **2012**.

[8] Nielsen, S. V.; Pedersen, E. B. Phosphorus pentoxide in organic synthesis. XXIX. Synthesis of 4-arylamino-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolines and the corresponding N-Mannich bases. *Liebigs. Ann. Chem.*, **1986**, *10*, 1728-1735.

[9] Narsaiah, B.; Sivaprasad, A.; Venkatarranam, R. V. A. A novel synthesis of 3,4-disubstituted 1H-pyrazolo[3,4-b]quinolines. *Synth. Commun*., **1991**, *21(15-16)*, 1611-1617.

[10] Lipson, V. V.; Karnozhitskaya, T. M.; Desenko, S. M.; Shishkina, S. V.; Shishkin, O. E.; Musatov, V. I. Reactions of α-aminoazoles with diethyl benzylidenemalonate. *Russ. J. Org. Chem.*, **2007**, *43(2)*, 249-255.