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FAST, SOLVENT-FREE, AND HIGHLY EFFICIENT SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDINES USING MICROWAVE IRRADIATION AND $KHSO_4$ AS A REUSABLE GREEN CATALYST

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Abstract – A simple, ecofriendly, and effective method was described for forming pyrazolo[3,4-*b*]pyridines from 5-aminopyrazoles and 3-formylchromones, in good to excellent yields, under microwave irradiation in solvent-free conditions using $KHSO_4$ as a reusable catalyst. Some noteworthy features of this method were its cleanliness, short reaction time, easy work-up, and broad substrate tolerance. The catalyst was reused several times without losing activity.

INTRODUCTION

Over past decades, as an important subset of pyrazolopyridines, pyrazolo[3,4-*b*]pyridine has emerged as a multivalent scaffold that is used as a substructure for numerous pharmaceutically active compounds. Some important pyrazolo[3,4-*b*]pyridines have been described as anxiolytic drugs, including Etazolate and Tracazolate,[1] a stimulator of soluble guanylate cyclase (*s*GC),[2] inhibitor of glycogen synthase kinase-3 (GSK-3),[3] inhibitor of a cyclin dependent kinase 1 (CDK1),[4] an anticancer agent,[5] and an antiviral (Figure 1).[6] It is for these pharmacological properties, coupled with the pharmaceutical and fine chemical industries' interest in synthetic processes, that greener and more efficient technology is sought for their syntheses.

Generally, the construction of pyrazolo[3,4-*b*]pyridines is via condensation/cyclization from 5-aminopyrazoles and appropriate 1,3-dicarbonyl compounds or α,β-unsaturated carbonyl compounds.[7] To facilitate transformations, a series of catalysts have been employed, including Me_3SiCl, $AlCl_3$, and $SnCl_4$.[8] Although their excellent performance as catalysts affords abundant compounds for subsequent biological investigations, there remains a need to search for better catalysts with regard to their toxicity, handling, availability, economic viability, and operational simplicity. In view of the recent trend in catalytic processes toward the development of clean and green chemical processes, investigations for new and less hazardous catalysts have become a priority in synthetic organic chemistry.[9]

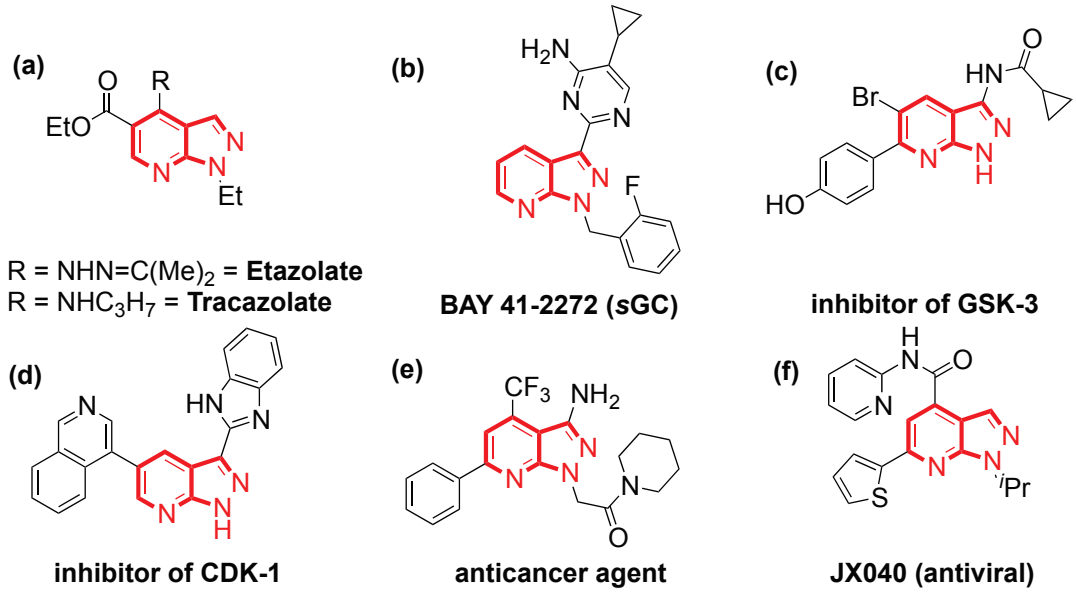


Figure 1. Examples of bioactive pyrazolo[3,4-*b*]pyridines

Over the last decade, microwave-assisted synthesis has become a major focus for many synthetic chemists due to its high-efficiency energy transfer, which agitates substrates to react much more readily.[10] Otherwise, the use of inorganic reagents in solvent-free conditions has rapidly increased in recent years, as these reactions often include milder reaction conditions, easier work-up, and higher selectivity than similar reactions using organic reagents in solution.[11]

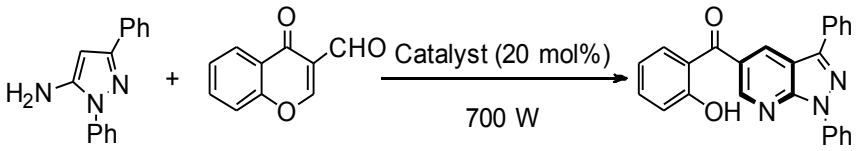
In continuation of our program to develop reactions in solvent-free systems and in catalytic manner,[12] herein, a simple and efficient protocol was reported for the preparation of functionalized pyrazolo[3,4-*b*]pyridines. Solvent-free microwave irradiation was employed with only a catalytic amount of $KHSO_4$, which is a relatively green chemical. Benefitted by its high efficiency, the protocol could be applied to synthesize various pyrazolo[3,4-*b*]pyridine derivatives for subsequent biological investigation.

RESULTS AND DISCUSSION

The synthesis of pyrazolo[3,4-*b*]pyridine derivative **3a** was chosen as the model reaction (Table 1). The reaction between 1,3-diphenyl-*1H*-pyrazol-5-amines **1a** and 3-formylchromone **2a** gave an acceptable yield of 74% after 10 min of microwave irradiation in the absence of any solvent or additive (Table 1, Entry 1). Significant improvement was observed when a comparative reaction was conducted under conventional solvent-free conditions, which produced an extremely low yield of 36% after 4 h of heating (Table 1, Entry 2). The model reaction was performed using 700 W microwave irradiation for 5 min without stirring. To improve the reaction further in an efficient manner, different salts were examined as catalysts (Table 1, Entries 3–9). Among the compounds screened, pyrazolo[3,4-*b*]pyridine derivative **3a** was obtained in excellent yield in the presence of $KHSO_4$ (Table 1, Entry 9). Different amounts of

$KHSO_4$ were then screened to seek better utilization (Table 1, Entries 10–12). The use of 20% $KHSO_4$ was used up and it was understandable that small amounts of $KHSO_4$ led to decreased yield. In this model, the best ratio of **1a**/**2a**/$KHSO_4$ was chosen to be 1/1/0.1 (by mol).

Table 1. Catalyst screen for pyrazolo[3,4-*b*]pyridine derivate synthesis[a]



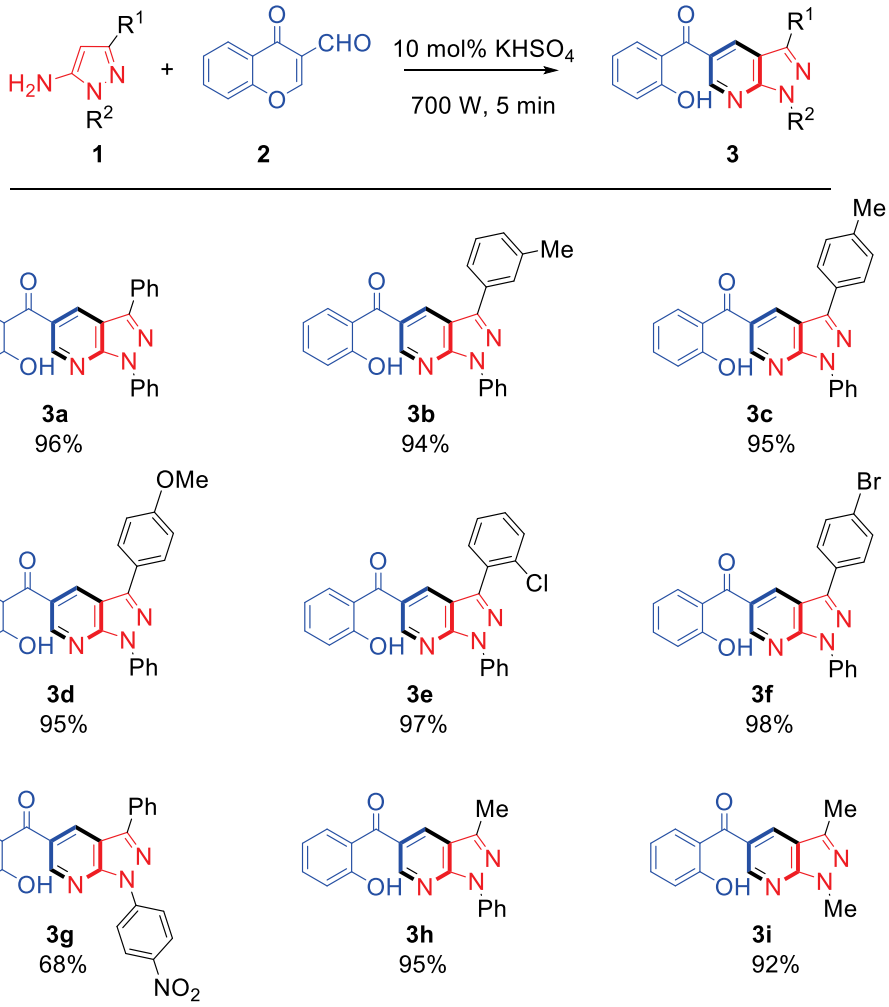
1a **2a** **3a**

Entry	Catalyst	Time (min)	Yield[b] (%)
1	/	10	74
2[c]	/	240	36
3	$NaHCO_3$	5	88
4	Na_2CO_3	5	81
5	$NaHSO_4$	5	90
6	Na_2SO_4	5	86
7	K_2SO_4	5	91
8	$KHCO_3$	5	88
9	$KHSO_4$	5	98
10[d]	***$KHSO_4$***	***5***	***97***
11[e]	$KHSO_4$	20	91
12[f]	$KHSO_4$	5	93

[a]Reactions were carried out with **1a** (1 mmol), **2a** (1 mmol), and catalyst (0.2 mmol) without solvent under microwave irradiation at 700 W. [b]Isolated yield. [c]Reaction was perfomed at 100 °C heated by oil bath. [d]0.1 mmol $KHSO_4$ was used. [e]0.02 mmol $KHSO_4$ was used. [f]0.05 mmol $KHSO_4$ was used.

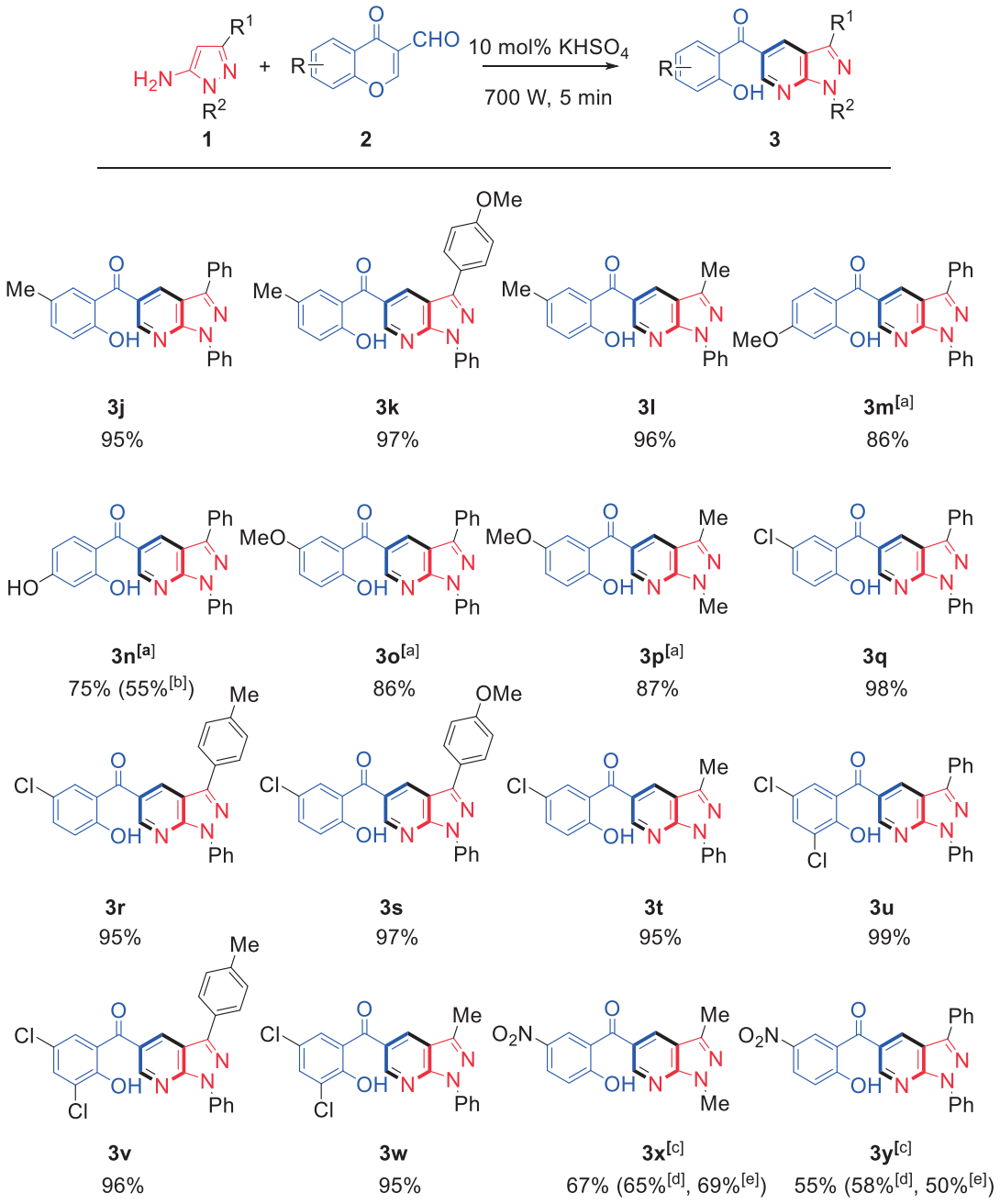
With the optimized conditions in hand, the scope of the reaction was then examined. Generally, the reaction proceeded smoothly giving the desired product in good yield within 5–10 min. First, a wide variety of 1,3-disubstituted-*1H*-pyrazol-5-amine was tested with 3-formylchromone **2a** (Scheme 1). The reactions of 1,3-diphenyl-*1H*-pyrazol-5-amines bearing either an electron-donating (Scheme 1, **3b**–**3d**) or electron-withdrawing substituent (Scheme 1, **3e** and **3f**) on the benzene ring proceeded smoothly, affording desired products in good yields. A significant decrease in yield was observed with nitro-substituted 5-aminopyrazole (Scheme 1, **3g**), which was explained by decreased nucleophilicity. In addition, 1-phenyl-3-methyl- and 1,3-dimethyl-*1H*-prrazol-5-amine (Scheme 1, **3h** and **3i**) were also

proven to be effective substrates, leading to the corresponding products in good yields. Generally, the electron cloud density of 5-aminopyrazole did not greatly influence the cycling reaction.



Scheme 1. 5-Aminopyrazole screen for the synthesis of pyrazolo[3,4-*b*]pyridines

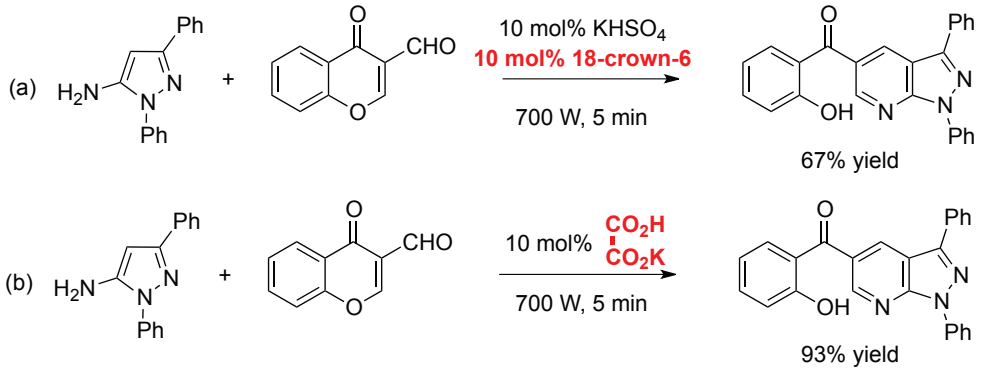
Second, attention was focused on expanding the scope of the 3-formylchromones (Scheme 2). It was found that the weak electron-donating group methyl did not greatly influence the reaction (Scheme 2, **3j**–**3l**). Alternatively, the substituted group methoxyl decreased the yield (Scheme 2, **3m**, **3o**, and **3p**), which was probably caused by its strong electron-conjugating effects. In particular, when there was a hydroxyl instead of methoxyl on a chromone, the yield suffered a further decrease (Scheme 2, **3n**). It was believed here that phenolic compounds could not withstand such severe reaction conditions and were partially oxidized. Also, halogen atoms, such as chlorine, did not show much impact on the reaction (Scheme 2, **3q**–**3w**). Furthermore, 6-nitro-3-formylchromone was reacted with 5-aminopyrazoles and it was gratifying that the desired compounds were generated, although the yields were greatly influenced by the nitro group (Scheme 2, **3x** and **3y**). A further experiment indicated that neither increasing the amount of $KHSO_4$ nor extending the reaction time was helpful for producing a better conversion rate.



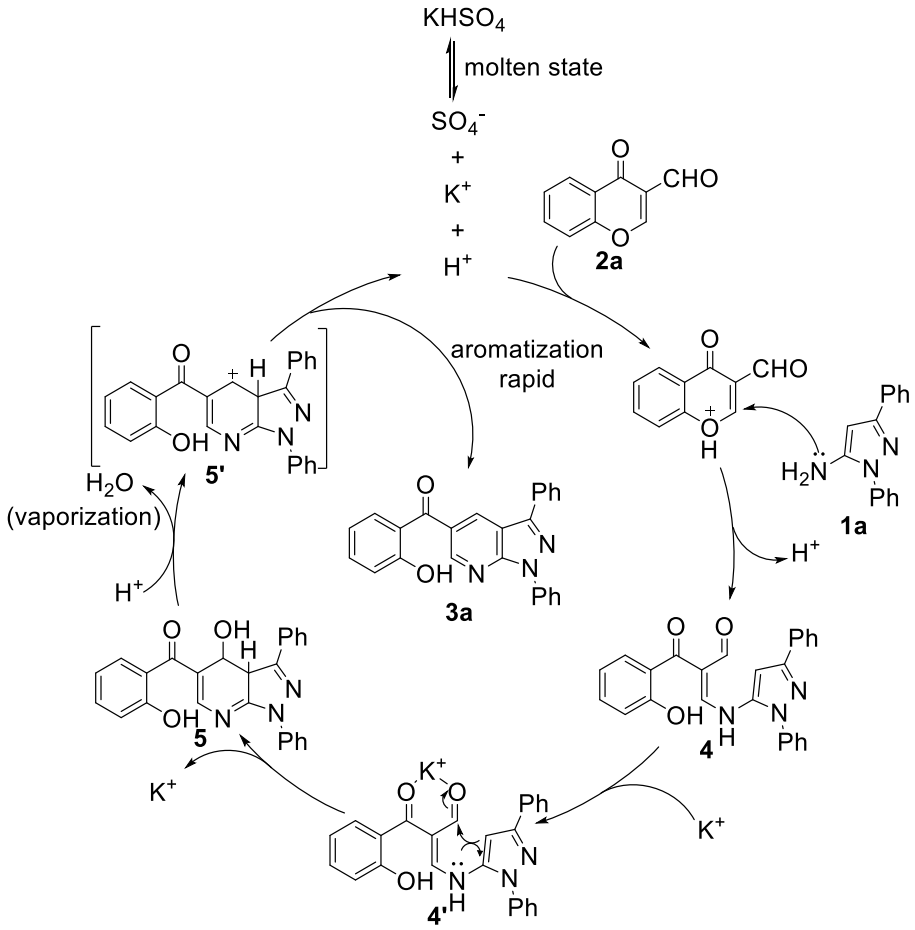
Scheme 2. 3-Formylchromone screen for the synthesis of pyrazolo[3,4-*b*]pyridines

[a]10 min. [b]550 W, 30 min. [c]0.1 mmol reaction scale employed due to the explosive nitrocompounds. [d]0.1 mmol (1.0 equiv.) $KHSO_4$. [e]30 min.

Control experiments were carried out to illuminate the role of $KHSO_4$ (Scheme 3). First, 18-crown-6 was used in the model reaction to peel off potassium ions, which led to a much lower yield of 67%, thus indicating that K^+ was critical in this reaction (Scheme 3, (a)). In addition, when potassium hydrogen oxalate was tested instead of $KHSO_4$, the yield was 93%, which indicated that sulfate ions were not necessary (Scheme 3, (b)).



Scheme 3. Control experiments



Scheme 4. Possible mechanism of reaction

According to the above experimental results and previous reports,[13] a plausible reaction mechanism was proposed (Scheme 4). First, when 3-formylchromone, 5-aminopyrazole, and $KHSO_4$ were mixed, a sufficient grinding insured a homogeneous system. Once the reaction was started, high energy from microwave irradiation melted the reactants and ionization of $KHSO_4$ provided H^+ and K^+ for the subsequent reactions. In the presence of H^+, the reaction between 5-aminopyrazole **1** and 3-formylchomone **2** underwent an intermolecular nucleophilic addition-elimination reaction resulting in

the enamine **4**. This **4** then captured K^+, forming complex **4′** that activated and polarized the aldehyde, leading to an intramolecular nucleophilic addition-elimination process and producing a cyclic intermediate **5**. Finally, a rapid dehydration of **5** was followed by aromatization of the resultant dicyclic carbocation **5′** to yield the pyrazolo[3,4-*b*]pyridine product **3**.

$KHSO_4$ was recycled and reused in the model reaction over five times with almost constant catalytic efficiency for constructing pyrazolo[3,4-*b*]pyridines. When the reaction was complete, the product **3a** was dissolved in hot ethyl acetate and the $KHSO_4$ then recycled by filtration and desiccation. The catalytic rate of the first recycling was 96% and the catalytic efficiency slightly reduced to 95% after the 5th recycling (Figure 2). The yield decreased to 92% after the 6th recycling. Further recovery was not performed because of the reduced efficiency, which might have been caused by the loss of $KHSO_4$ during processing. In this study, $KHSO_4$ was found to possess great potential for reuse in the synthesis of various pyrazolo[3,4-*b*]pyridine derivatives, thus decreasing processing costs and achieving green chemistry.

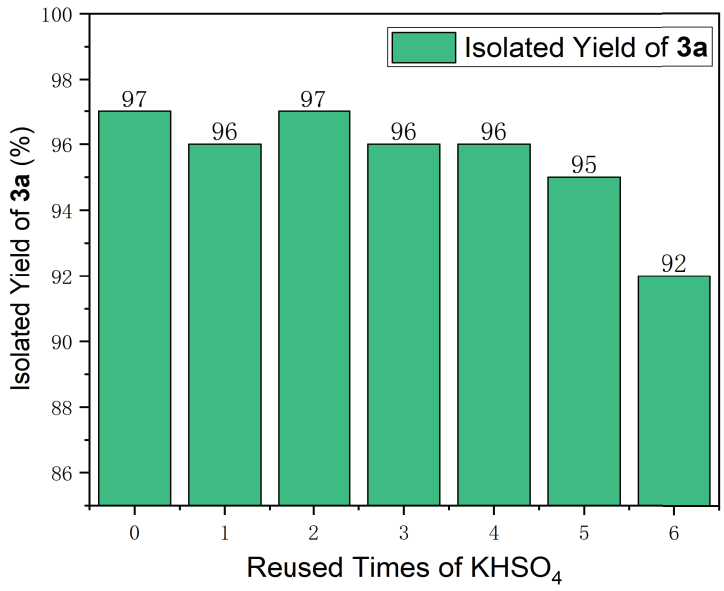


Figure 2. Recycling of $KHSO_4$ for constructing pyrazolo[3,4-*b*]pyridines

EXPERIMENTAL

All reagents were purchased from commercial sources and were used as received, unless otherwise indicated. All used silica gel is 300 mesh (Qingdao Haiyang Chemical Co., Ltd.). TLC analysis was performed using precoated glass plates. A domestic microwave oven (LG WD700, LG Tianjin Electronics Co., Ltd.) was employed. All of the microwave reactions were performed in 25 mL ceramic crucibl. Melting points (mp) were obtained on a digital melting point apparatus (BUCHI M-565) and are uncorrected. NMR spectra were recorded with a 400 (or 600) MHz spectrometer for ^{1}H NMR and 101 (or

151) MHz for ^{13}C NMR, and TMS was used as an internal standaed. Mass spectra were recorded with a HRMS-ESI-Q-TOF (Agilent 6210 TOF LC/MS or micrOTOF-Q II) and a low-resolution MS instrument (Finnigan Trace DSQ) using an ESI ion source.

General Procedure for the synthesis of pyrazolo[3,4-*b*]pyridine derivates 3

To a ceramic crucible were added **1** (0.470 g, 2 mmol), **2** (0.348 g, 2 mmol), and $KHSO_4$ (0.027 g, 0.2 mmol) and the mixture was reacted under microwave irradiation at 700 W for 5 min. The resulting reaction mixture was dissolved in hot EtOAc, immediately filtered, and the filtrate directly purified by crystallization at -5 °C to yield the desired product **3.**

(1,3-Diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxyphenyl)methanone (3a)[8c]

White solid; Yield (0.759 g, 1.94 mmol, 97%); mp 166.4 – 167.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.4, 1H), 7.50 – 7.46 (m, 1H), 7.63 – 7.53 (m, 6H), 8.03 (d, J = 7.2, 2H), 8.34 (d, J = 8.0, 2H), 8.76 (s, 1H), 8.98 (s, 1H), 11.85 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.8, 118.9, 119.3, 119.4, 121.8, 121.9, 126.8, 127.6, 128.3, 129.3, 129.3, 129.4, 132.0, 132.9, 133.2, 136.9, 139.0, 145.8, 150.0, 151.7, 163.3, 198.7; MS (ESI) *m/z* 390 [$(M-H)^-$].

(2-Hydroxyphenyl)(1-phenyl-3-(*m*-tolyl)-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3b)

White solid; Yield (0.761 g, 1.88 mmol, 94%); mp 217.5 – 218 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 6.92 (t, J = 7.2, 1H), 7.12 (d, J = 7.6, 1H), 7.29 (d, J = 7.6, 1H), 7.45 – 7.35 (m, 2H), 7.63 – 7.55 (m, 4H), 7.80 (d, J = 7.6, 1H), 7.85 (s, 1H), 8.34 (d, J = 8.8, 2H), 8.75 (s, 1H), 8.97 (s, 1H), 11.86 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 29.8, 112.4, 116.1, 117.2, 119.3, 121.2, 124.6, 124.8, 125.1, 126.4, 127.8, 129.0, 130.3, 131.1, 132.5, 135.3, 138.7, 146.2, 150.6, 152.1, 152.6, 161.3; HRMS (FTMS + pESI): calcd for $C_{26}H_{20}N_3O_2$ [$(M+H)^+$] 406.1556, found 406.1548.

(5-Chloro-2-hydroxyphenyl)(1-phenyl-3-(*p*-tolyl)-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3c)

White solid; Yield (0.834 g, 95%); mp 152.1 – 153.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.08 (d, J = 9.2), 7.37 (m, 3H), 7.64 – 7.46 (m, 4H), 7.92 (d, J = 8.0, 2H), 8.32 (d, J = 7.6, 2H), 8.75 (s, 1H), 8.95 (s, 1H,), 11.72 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.9, 115.0, 120.0, 120.5, 121.8, 124.0, 126.9, 127.5, 129.0, 129.3, 130.0, 132.0, 133.2, 136.7, 138.9, 139.6, 146.0, 149.8, 151.8, 161.6, 197.7; HRMS (FTMS + pESI): calcd for $C_{26}H_{19}ClN_3O_2$ [$(M+H)^+$] 440.1166, found 440.1152.

(2-Hydroxyphenyl)(3-(4-methoxyphenyl)-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3d)

Light yellow solid; Yield (0.800 g, 1.80 mmol, 95%); mp 162.1 – 163.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.93 (t, J = 7.6, 1H), 7.07 (d, J = 8.8, 2H), 7.13 (d, J = 8.4, 1H), 7.36 (t, J = 7.6, 1H), 7.64

– 7.55 (m, 4H), 7.98 (d, *J* = 8.8, 2H), 8.34 (d, *J* = 7.6, 2H), 8.74 (s, 1H),8.97 (s, 1H), 11.86 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.4, 114.6, 118.7, 119.1, 119.2, 121.6, 124.5, 126.6, 127.9, 128.7, 129.2, 132.8, 133.0, 136.7, 138.9, 145.6, 149.9, 151.6, 160.5, 163.2, 198.8; HRMS (FTMS + pESI): calcd for $C_{26}H_{20}N_3O_3$ [$(M+H)^+$] 422.1512, found 422.1505.

(3-(2-Chlorophenyl)-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxyphenyl)methanone (3e)

Light yellow solid; Yield (0.825 g, 1.94 mmol, 97%); mp 188.7 – 189.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (t, *J* = 8.0, 1H), 7.10 (d, *J* = 8.4, 1H), 7.38 (t, *J* = 7.6, 1H), 7.46–7.43 (m, 2H), 7.60 – 7.54 (m, 4H), 7.64 (d, *J* = 8.0, 1H), 7.72 – 7.00 (m, 1H), 8.33 (d, *J* = 7.6, 2H), 8.51 (s, 1H), 9.01 (s, 1H), 11.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 115.2, 118.6, 118.9, 119.0, 121.6, 126.7, 127.1, 127.7, 129.1, 130.2, 130.5, 130.6, 132.1, 133.0, 133.5, 136.6, 138.6, 144.6, 149.9, 150.9, 162.9, 198.5; HRMS (FTMS + pESI): calcd for $C_{25}H_{17}ClN_3O_2$ [$(M+H)^+$] 426.1015, found 426.1009.

(3-(4-Bromophenyl)-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxyphenyl)methanone (3f)

Brown solid; Yield (0.919 g, 1.96 mmol, 98%); mp 188.5 – 189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (m, 1H), 7.14 (d, *J* = 8.4, 1H), 7.40 (t, *J* = 7.2, 1H), 7.71-7.56 (m, 6H), 7.94 (d, *J* = 8.4, 2H), 8.32 (d, *J* = 7.6, 2H), 8.74 (s, 1H), 9.00 (s, 1H), 11.86 (s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.4, 118.8, 119.1, 119.2, 121.7, 123.6, 127.0, 128.3, 128.8, 129.4, 130.8, 132.4, 132.5, 133.0, 136.9, 138.7, 144.6, 150.1, 151.7, 163.2, 198.7; HRMS (FTMS + pESI): calcd for $C_{25}H_{17}BrN_3O_2$ [$(M+H)^+$] 470.0511, found 470.0504.

(2-Hydroxyphenyl)(1-(4-nitrophenyl)-3-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3g)

Yellow solid; Yield (0.593 g, 1.36 mmol, 68%); mp 204.8 – 205.3 °C (petroleun ether/EtOAc = 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (ddd, *J* = 8.2, 7.2, 1.2, 1H), 7.18 (dd, *J* = 8.4, 1.1, 1H), 7.58 – 7.55 (m, 1H), 7.62 (tdd, *J* = 7.6, 5.8, 1.8, 4H), 8.10 – 8.04 (m, 2H), 8.49 – 8.44 (m, 2H), 8.82 (d, *J* = 2.0, 1H), 8.87 – 8.84 (m, 2H), 9.06 (d, *J* = 2.0, 1H), 11.86 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 115.7, 118.9, 119.1, 119.3, 120.4, 125.0, 127.6, 129.2, 129.3, 130.0, 131.1, 132.8, 132.9, 138.1, 144.1, 145.1, 147.4, 150.2, 152.4, 163.3, 198.5; HRMS (FTMS + pESI): calcd for $C_{25}H_{15}N_4O_4$ [$(M+H)^+$] 435.1112, found 435.1099.

(2-Hydroxyphenyl)(3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3h)[8c]

White solid; Yield (0.625 g, 1.90 mmol, 95%); mp 117.6 – 118.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 6.95 (t, *J* = 8.0, 1H), 7.13 (d, *J* = 7.6, 1H), 7.35 (t, *J* = 7.6, 1H), 7.60 – 7.53 (m, 3H), 7.63 (d, *J* = 8.0, 1H), 8.25 (d, *J* = 7.6, 2H), 8.47 (s, 1H),8.97 (s, 1H), 11.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.5, 116.3, 118.7, 119.0, 119.2, 121.2, 126.3, 127.2, 129.2, 131.7, 133.0, 136.6, 138.9, 144.3, 150.1, 151.2, 163.1, 198.8; MS (ESI) *m/z* 330 [$(M+H)^+$].

(1,3-Dimethyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxyphenyl)methanone (3i)

White Solid; Yield (0.491 g, 1.84 mmol, 92%); mp 144.8 – 145.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.64 (s, 3H), 4.17 (s, 3H), 6.96 (ddd, J = 8.2, 7.3, 1.2 Hz, 1H), 7.14 (dd, J = 8.5, 1.1 Hz, 1H), 7.58 (ddd, J = 8.6, 7.2, 1.7, 1H), 7.62 (dd, J = 8.0, 1.7, 1H), 8.41 (d, J = 2.0, 1H), 8.91 (d, J = 2.0, 1H), 11.88 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 13.0, 34.2, 113.9, 118.3, 118.5, 119.0, 125.8, 131.3, 132.5, 135.9, 141.9, 149.2, 162.3, 198.0; HRMS (FTMS + pESI): calcd for $C_{15}H_{14}N_3O_2$ [$(M+H)^+$] 268.1081, found 268.1068.

(1,3-Diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-5-methylphenyl)methanone (3j)

Light yellow solid; Yiled (0.770 g, 1.90 mmol, 95%); mp 130.7 – 131.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 7.03 (d, J = 8.4, 1H), 7.60 – 7.36 (m, 8H), 8.05 (d, J = 7.2, 2H), 8.34 (d, J = 8.0, 2H), 8.78 (s, 1H), 8.97 (s, 1H), 11.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6, 114.6, 118.3, 118.8, 121.5, 126.6, 127.3, 128.1, 129.0, 131.7, 132.6, 137.6, 138.7, 145.5, 149.6, 161.4, 160.9, 198.3; HRMS (FTMS + pESI): calcd for $C_{26}H_{20}N_3O_2$ [$(M+H)^+$] 406.1556, found 406.1548.

(2-Hydroxy-5-methylphenyl)(3-(4-methoxyphenyl)-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3k)[14a]

Light yellow solid; Yield (0.818 g, 1.88 mmol, 94%); mp 159.3 – 160.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.89 (s, 3H), 7.07 – 7.00 (m, 3H), 7.39 – 7.40 (m, 3H), 7.58 – 7.54 (m, 2H), 7.98 (d, J = 8.8, 2H), 8.32 (d, J = 7.6, 2H), 8.74 (s, 1H), 8.94 (s, 1H), 11.67 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.7, 55.4, 114.4, 118.2, 118.7, 121.2, 121.4, 124.3, 126.4, 127.8, 128.0, 128.6, 129.1, 132.6, 137.6, 138.7, 145.2, 149.6, 151.3, 160.2, 160.8, 198.2; MS (ESI) *m/z* 436 [$(M+H)^+$].

(2-Hydroxy-5-methylphenyl)(3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3l)[14a]

Yellow solid; Yield (0.659 g, 1.92 mmol, 96%); mp 121.1 – 122.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.71 (s, 3H), 7.02 (d, J = 8.0, 1H), 7.37 – 7.31 (m, 3H), 7.53 (t, J = 8.0, 2H), 8.23 (d, J = 8.0, 2H), 8.45 (s, 1H), 8.92 (s, 1H), 11.65 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6, 12.6, 20.6, 116.3, 118.3, 118.8, 121.0, 126.1, 127.2, 128.0, 129.0, 131.5, 132.5, 137.5, 138.7, 144.1, 149.8, 150.9, 160.8, 198.4; MS (ESI) *m/z* 342 [$(M-H)^-$].

(1,3-Diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-4-methoxyphenyl)methanone (3m)

Brown solid; Yield (0.362 g, 1.72 mmol, 86%); mp 172.7 – 173.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.44 (dt, J = 9.2, 3.1, 1H), 6.55 (t, J = 2.5, 1H), 7.36 (t, J = 7.8, 1H), 7.58 – 7.45 (m, 5H), 8.02 (d, J = 8.0, 2H), 8.33 (d, J = 8.1, 2H), 8.70 (s, 1H), 8.92 (s, 1H), 12.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.8, 101.8, 113.4, 114.6, 121.6, 122.5, 126.5, 127.4, 128.6, 129.0, 129.1, 129.3, 132.1, 134.6, 139.0, 149.5, 166.3, 166.5, 196.8; HRMS (FTMS + pESI): calcd for $C_{26}H_{20}N_3O_3$ [$(M+H)^+$] 422.1499, found

422.1488.

(2,4-Dihydroxyphenyl)(1,3-diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3n)

Yellow solid; Yield (0.611 g, 1.50 mmol, 75%); mp 135.8 – 136.4 °C (petroleun ether/EtOAc = 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.44 – 6.41 (m, 2H), 7.43 (ddd, J = 8.7, 6.9, 1.3, 1H), 7.53 (dd, J = 8.6, 6.1, 2H), 7.60 (td, J = 7.7, 1.8, 2H), 7.66 – 7.62 (m, 2H), 8.13 (dd, J = 7.3, 1.9, 2H), 8.35 (dq, J = 7.3, 1.0, 2H), 8.86 – 8.85 (m, 1H), 8.96 – 8.93 (m, 1H), 10.74 (s, 1H), 11.83 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 103.2, 109.0, 114.10, 114.11, 121.7, 127.8, 129.6, 129.71, 129.76, 129.8, 131.9, 132.9, 135.7, 139.0, 145.5, 150.4, 151.5, 164.0, 165.3, 196.0; HRMS (FTMS + pESI): calcd for $C_{25}H_{16}N_3O_3$ [(M-H)$^-$] 406.1212, found 406.1197.

(1,3-Diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-5-methoxyphenyl)methanone (3o)

Light yellow solid; Yield (0.362 g, 1.72 mmol, 86%); mp 162.4 – 162.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (s, 3H), 7.13 – 7.09 (m, 2H), 7.23 (dd, J = 9.1, 3.0, 1H), 7.42 (tt, J = 7.4, 1.2, 1H), 7.54 – 7.51 (m, 1H), 7.64 – 7.57 (m, 4H), 8.10 – 8.06 (m, 2H), 8.39 (dd, J = 8.7, 1.2, 2H), 8.84 (d, J = 2.0, 1H), 9.04 (d, J = 2.0, 1H), 11.48 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 56.0, 114.8, 115.5, 118.8, 119.7, 121.8, 124.8, 126.8, 127.5, 128.3, 129.21, 129.25, 129.4, 131.9, 132.8, 138.9, 145.8, 149.9, 151.7, 151.8, 157.6, 198.4; HRMS (FTMS + pESI): calcd for $C_{26}H_{18}N_3O_3$ [(M-H)$^-$] 420.1354, found 420.1351.

(1,3-Dimethyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-5-methoxyphenyl)methanone (3p)

White solid; Yield (0.259 g, 1.74 mmol, 87%); mp 94.0 – 94.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.74 (s, 3H), 4.16 (s, 3H), 7.09 – 7.06 (m, 2H), 7.20 (dd, J = 9.1, 3.0, 1H), 8.43 (d, J = 2.0, 1H), 8.92 (d, J = 2.0, 1H), 11.40 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 12.5, 33.8, 56.0, 114.3, 115.7, 118.9, 119.5, 124.2, 126.3, 131.8, 142.6, 159.8, 151.69, 151.71, 157.3, 198.7; HRMS (FTMS + pESI): calcd for $C_{16}H_{14}N_3O_3$ [(M-H)$^-$] 296.1041, found 296.1027.

(5-Chloro-2-hydroxyphenyl)(1,3-diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3q)

Light yellow solid; Yield (0.833 g, 1.96 mmol, 98%); mp 185.2 – 186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.8, 1H), 7.38 (t, J = 7.6, 1H), 7.62 – 7.47 (m, 7H), 8.03 (d, J = 7.2, 2H), 8.33 (d, J = 7.6, 2H), 8.78 (s, 1H), 8.96 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 114.7, 119.8, 120.3, 121.7, 123.8, 126.8, 127.4, 129.1, 129.3, 131.7, 132.8, 136.5, 138.6, 145.7, 149.6, 151.6, 161.4, 197.5; HRMS (FTMS + pESI): calcd for $C_{25}H_{17}ClN_3O_2$ [(M+H)$^+$] 426.1015, found 426.1009.

(5-Chloro-2-hydroxyphenyl)(1-phenyl-3-(*p*-tolyl)-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3r)

White solid; Yield (0.834 g, 1.90 mmol, 95%); mp 152.1 – 153.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45

(s, 3H), 7.08 (d, *J* = 9.2, 1H), 7.37 (m, 3H), 7.64 – 7.46 (m, 4H), 7.92 (d, *J* = 8.0, 2H), 8.32 (d, *J* = 7.6, 2H), 8.75 (s, 1H), 8.95 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 21.9, 115.0, 120.0, 120.5, 121.8, 124.0, 126.9, 127.5, 129.0, 129.3, 130.0, 132.0, 133.2, 136.7, 138.9, 139.6, 146.0, 149.8, 151.8, 161.6, 197.7; HRMS (FTMS + pESI): calcd for $C_{26}H_{19}ClN_3O_2$ [$(M+H)^+$] 440.1166, found 440.1152.

(5-Chloro-2-hydroxyphenyl)(3-(4-methoxyphenyl)-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3s)

Light yellow solid; Yield (0.883 g, 1.94 mmol, 97%); mp 161.1 – 162.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.89 (s, 3H), 7.08 – 7.05 (m, 3H), 7.36 (t, *J* = 8.0, 1H), 7.60 – 7.48 (m, 4H), 7.96 (d, *J* = 8.4, 2H), 8.31 (d, *J* = 8.4, 2H), 8.73 (s, 1H), 8.93 (s, 1H), 11.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 55.4, 114.4, 119.7, 120.2, 121.4, 123.6, 124.1, 126.5, 127.1, 128.5, 129.0, 131.6, 132.8, 136.3, 138.6, 145.4, 149.5, 151.4, 160.3, 161.3, 197.3; HRMS (FTMS + pESI): calcd for $C_{26}H_{19}ClN_3O_2$ [$(M+H)^+$] 456.1123, found 456.1115.

(5-Chloro-2-hydroxyphenyl)(3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3t)[14b]

White solid; Yield (0.690 g, 1.90 mmol, 95%); mp 152.1 – 153.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.72 (s, 3H), 7.08 (d, *J* = 9.2, 1H), 7.33 (t, *J* = 7.6, 1H), 7.58 – 7.48 (m, 4H), 8.22 (d, *J* = 8.0, 2H), 8.44 (s, 1H), 8.92 (s, 1H), 11.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 12.7, 116.3, 119.7, 120.2, 121.1, 123.6, 126.3, 126.4, 129.0, 131.6, 136.3, 138.6, 149.7, 151.0, 161.3, 197.5; MS (ESI) *m/z* 362 [$(M-H)^-$].

(3,5-Dichloro-2-hydroxyphenyl)(1,3-diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3u)

Light yellow solid; Yield (0.909 g, 1.98 mmol, 99%); mp 189.8 – 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.39 (t, *J* = 7.6, 1H), 7.60 – 7.48 (m, 7H), 8.03 (d, *J* = 7.2, 2H), 8.32 (d, *J* = 7.6, 2H), 8.79 (s, 1H), 8.95 (s, 1H), 12.16 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 114.8, 120.3, 121.6, 121.8, 123.6, 124.3, 126.8, 127.0, 127.2, 127.5, 129.0, 129.2, 130.2, 130.4, 131.5, 133.1, 135.9, 136.1, 138.5, 145.7, 149.6, 151.5, 157.1, 197.2; HRMS (FTMS + pESI): calcd for $C_{25}H_{16}Cl_2N_3O_2$ [$(M+H)^+$] 460.0633, found 460.0620.

(3,5-Dichloro-2-hydroxyphenyl)(1-phenyl-3-(*p*-tolyl)-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone-(3v)

Light yellow solid; Yield (0.754 g, 1.90 mmol, 95%); mp 189.4 – 189.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*2.45 (s, 3H), 7.42 – 7.33 (m, 3H), 7.61 – 7.52 (m, 3H), 7.64 (d, *J* = 2.4, 1H), 7.91 (d, *J* = 7.6 , 2H), 8.31 (d, *J* = 7.6, 2H), 8.76 (d, *J* = 2.0, 1H), 8.93 (d, *J* = 2.0, 1H), 12.16 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 21.6, 114.7, 120.3, 121.5, 123.5, 124.2, 126.7, 127.1, 128.6, 129.0, 129.2, 130.3, 133.0, 135.9, 138.5, 139.4, 145.8, 149.5, 151.5, 157.1, 197.1; HRMS (FTMS + pESI): calcd for $C_{20}H_{14}Cl_2N_3O_2$ [$(M+H)^+$] 398.0463, found 398.0452.

(3,5-Dichloro-2-hydroxyphenyl)(3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)methanone (3w)

Light yellow solid; Yield (0.754 g, 1.90 mmol, 95%); mp 219.3 – 220.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 3H), 7.34 (t, J = 7.6, 1H), 7.57–7.51 (m, 3H), 7.64 (s, 1H), 8.21 (d, J = 7.6, 2H), 8.46 (s, 1H), 8.92 (s, 1H), 12.16 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.7, 116.4, 120.4, 121.2, 123.5, 124.3, 126.1, 129.1, 130.3, 131.8, 135.8, 138.5, 144.4, 149.7, 151.1, 157.1, 197.3; HRMS (FTMS + pESI): calcd for $C_{20}H_{14}Cl_2N_3O_2$ [$(M+H)^+$] 398.0463, found 398.0459.

(1,3-Dimethyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-5-nitrophenyl)methanone (3x)

Yellow solid; Yield (21 mg, 0.067 mmol, 67%); mp 204.8 – 205.3 °C (petroleun ether/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.19 (s, 3H), 7.26 (d, J = 9.2, 1H), 8.47 – 8.43 (m, 2H), 8.63 (d, J = 2.0, 1H), 8.93 (d, J = 2.0, 1H), 12.53 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 12.5, 33.9, 114.5, 118.3, 119.8, 124.8, 129.0, 131.0, 132.1, 139.6, 143.0, 149.6, 151.9, 167.7, 198.2; HRMS (FTMS + pESI): calcd for $C_{15}H_{11}N_4O_4$ [$(M-H)^-$] 311.0787, found 311.0786.

(1,3-Diphenyl-*1H*-pyrazolo[3,4-*b*]pyridin-5-yl)(2-hydroxy-5-nitrophenyl)methanone (3y)

Brown solid; Yield (24 mg, 0.055 mmol, 55%); mp 153.6 – 154.4 °C (petroleun ether/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 9.2, 1H), 7.46 – 7.41 (m, 1H), 7.55 – 7.51 (m, 1H), 7.64 – 7.58 (m, 4H), 8.08 – 8.05 (m, 2H), 8.40 – 8.36 (m, 2H), 8.47 (dd, J = 9.2, 2.7, 1H), 8.72 (d, J = 2.7, 1H), 8.84 (d, J = 2.1, 1H), 9.05 (d, J = 2.1, 1H), 12.56 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 114.9, 118.1, 119.9, 121.83, 121.84, 126.7, 127.0, 127.6, 129.0, 129.3, 129.5, 131.2, 131.6, 133.3, 138.7, 139.7, 146.2, 149.8, 151.9, 167.9, 197.8; HRMS (FTMS + pESI): calcd for $C_{25}H_{15}N_4O_4$ [$(M-H)^-$] 435.1099, found 435.1088.

General procedure using 18-crown-6 (Scheme 3, (a))

To a ceramic crucible were added 1,3-diphenyl-*1H*-pyrazol-5-amines **1a** (0.470 g, 2 mmol), 3-formylchromone **2a** (0.348 g, 2 mmol), $KHSO_4$ (0.027 g, 0.2 mmol), and 18-crown-6 (0.053 g, 0.2 mmol), and the mixture was reacted under microwave irradiation at 700 W for 5 min. The resulting reaction mixture was dissolved in hot EtOAc, immediately filtered, and the filtrate directly purified by crystallization at -5 °C to yield the desired product **3a** (0.524 g, 1.34 mmol, 67%) as white solid.

General procedure using potassium hydrogen oxalate (Scheme 3, (b))

To a ceramic crucible were added 1,3-diphenyl-*1H*-pyrazol-5-amines **1a** (0.470 g, 2 mmol), 3-formylchromone **2a** (0.348 g, 2 mmol), and potassium hydrogen oxalate (0.026 g, 0.2 mmol), and the mixture was reacted under microwave irradiation at 700 W for 5 min. The resulting reaction mixture was dissolved in hot EtOAc, immediately filtered, and the filtrate directly purified by crystallization at -5 °C to yield the desired product **3a** (0.728 g, 1.86 mmol, 93%) as white solid.

Recovery of the catalyst $KHSO_4$

Reusability of the $KHSO_4$ catalyst was investigated by the reaction of **1a** with **2a** using general procedure for **3**. Upon completion of the reaction, the resulting mixture was dissolved in hot EtOAc, and the $KHSO_4$ catalyst was separated from the solution using filtration. The catalyst was then washed with hot EtOAc (3 × 5 mL). Aftere drying under vacuum at 80 °C for 2 h, the catalyst could be recycled completely, and reused directly without further purification in the next run. The catalyst could be recycled for five runs withou the obvious loss of activity (Figure 2).

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