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Synthesis of Novel Substituted Pyridine Derivatives from 3,5-Diacetyl-2,6-dimethylpyridine

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ABSTRACT: *A series of novel (1-acetyl-5-aryl-4,5-dihydro)-1H-pyrazole substituted pyridine derivatives and poly substituted [2,3′-bipyridine]-5-carbonitrile derivatives were synthesized from 3,5-diacetyl-2,6-dimethylpyridine. The structures of two typical 3,5-bis[1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridines [***3b(1)*** and* ***3b(2)****] were confirmed by X-ray diffraction analysis.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:123–130, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20522

INTRODUCTION

Pyrazolines have been reported showing a wide spectrum of biological activity [1–4]. 1-Acetyl-4,5-dihydro-1*H*-pyrazole derivatives showed to be potent and selective monoamine oxidase-A inhibitors and probably to be a novel class of small-molecule necroptosis inhibitors [5–7].

Many 3-pyridinecarbonitriles were used as dyes for synthetic fabrics and paper [8,9]. Benzothiepinopyridine derivatives have been reported the importance of valuable pharmacology [10,11]. A cyano group bonded to 3-position of pyridine ring of benzothiepinopyridine derivatives was found to be an anticancer as well as an anti-HIV active agent [12]. A methoxy group at the 2-position of benzothiepinopyridine-3-carbonitrile improved total observed pharmacological properties [13].

In this study, we utilized 3,5-diacetyl-2,6-dimethylpyridine **1** as a versatile precursor, which first reacted with aryl aldehydes to give α,β-unsaturated ketones by Aldol condensation and then by cyclization with hydrazine hydrate to generate a series of 3,5-bis(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-2,6-dimethylpyridines **3a–h**. Next, **1** reacted with 2-arylidenemalononitrile through Michael addition, followed by cyclization of a nucleophilic attack by methoxy anion to give a series of 5′-acetyl-4-aryl-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile **4a–h**. Synthetic routes are illustrated as following (Scheme 1).

RESULTS AND DISCUSSION

It is well known that α,β-unsaturated ketones are versatile precursors for the syntheses of the corresponding pyrazoline derivatives. Synthesis of the

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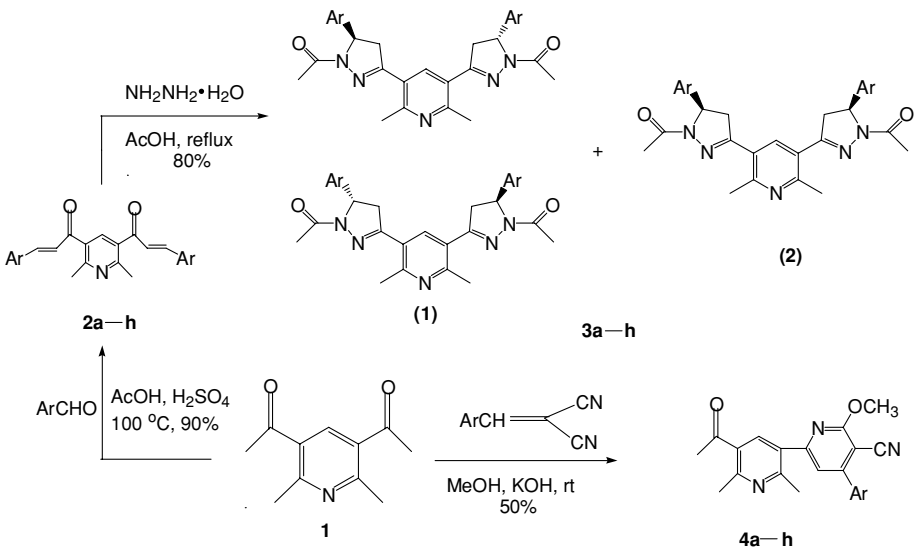

Ar: **3a** = C_6H_5, **3b** = 4-Cl-C_6H_4, **3c** = 3-Cl-C_6H_4, **3d** = 2-Cl-C_6H_4, **3e** = 2,4-Cl_2-C_6H_3, **3f** = 2-F-C_6H_4,

3g = 4-CH_3O-C_6H_4, **3h** = 4-O_2N-C_6H_4.

4a = 4-Cl-C_6H_4, **4b** = C_6H_5, **4c** = 4-$(CH_3)_2N$-C_6H_4, **4d** = 4-CH_3O-C_6H_4, **4e** = 4-HO-C_6H_4,

4f = 2-Furyl-, **4g** = 3,4-$(CH_3O)_2$-C_6H_3, **4h** = 2,4-Cl_2-C_6H_3.

SCHEME 1 Synthetic routes of **3a–h** and **4a–h**.

α,β-unsaturated ketones **2** by the Aldol condensation from 3,5-diacetyl-2,6-dimethylpyridine was first reported by Pavel and Antonin in 1992 [14]. However, the reported method suffered from low yields (5–68%) [14]. We modified the reaction conditions by adding the stoichiometric amount of condensed sulfuric acid in acetic acid as reaction solvent. The corresponding products **2** were obtained in 80–90% yields.

In the process of synthesizing of (1-acetyl-4,5-dihydro-1*H*-pyrazole)-substituted pyridines **3**, the mixture of **2** and 85% hydrazine hydrate were refluxed in acetic acid to afford the enantiomers **3**(**1**) and mesomer **3**(**2**) with different R_f value on thin-layer chromatography (TLC) plate, which could be separated by column chromatography. The generality of this reaction was investigated under the same reaction conditions. When we carried out the reactions with diverse α,β-unsaturated ketones, most of reactions proceeded smoothly and the target products were successfully obtained in moderate to good yields. The reaction results are summarized in Table 1. The yield ratio of **3**(**1**) and **3**(**2**) was 1:1 approximately. It was clear that the different substituted groups of aryl aldehydes had slight effect on the product distributions and yields.

The amount of 85% hydrazine hydrate was also screened. The complete conversion was observed, and the reaction gave higher yields when 2 equiv of 85% hydrazine hydrate was employed.

It should be indicated that in acetic acid media, the reaction directly afforded 1-acylated products and no pyrazolines were detected. To further study the possibility of formation of pyrazolines, a variety of solvents such as EtOH, THF, CH_3CN, DMF, PhMe, and DCM were selected. Unfortunately, the reactions were unsuccessful and TLC analysis showed that the reactions were complex.

The structures of two typical 3,5-bis[1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-2,6-dimethylpyridine [**3b**(**1**) and **3b**(**2**)] were confirmed by X-ray diffraction analysis (Fig. 1) [15,16]. **3b**(**1**) were racemic mixtures and **3b**(**2**) was a meso compound. For the racemic mixtures **3b**(**1**), their configurations of C-5 of 1-acetyl pyrazole ring are (*R, R*) or (*S, S*); whereas for the pure meso compound, the corresponding configuration of C-5 of 1-acetyl pyrazole ring is (*R, S*). It was obvious

TABLE 1 Synthesis of 3,5-Bis(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-2,6-dimethylpyridine[a]

Entry	*Ar*	*Product*	*Yield (%)*[b]	*Product*	*Yield (%)*[b]
1	C_6H_5	**3a**(**1**)	38	**3a**(**2**)	37
2	4-Cl-C_6H_4	**3b**(**1**)	43	**3b**(**2**)	40
3	3-Cl-C_6H_4	**3c**(**1**)	42	**3c**(**2**)	39
4	2-Cl-C_6H_4	**3d**(**1**)	39	**3d**(**2**)	37
5	2,4-Cl_2-C_6H_3	**3e**(**1**)	41	**3e**(**2**)	39
6	2-F-C_6H_4	**3f**(**1**)	43	**3f**(**2**)	41
7	4-CH_3O-C_6H_4	**3g**(**1**)	41	**3g**(**2**)	40
8	4-O_2N-C_6H_4	**3h**(**1**)	39	**3h**(**2**)	35

[a]Reaction conditions: α,β-unsaturated ketones (1 mmol), 85% hydrazine hydrate (2 mmol); solvent: acetic acid; refluxed, 8 h.
[b]Isolated yield.

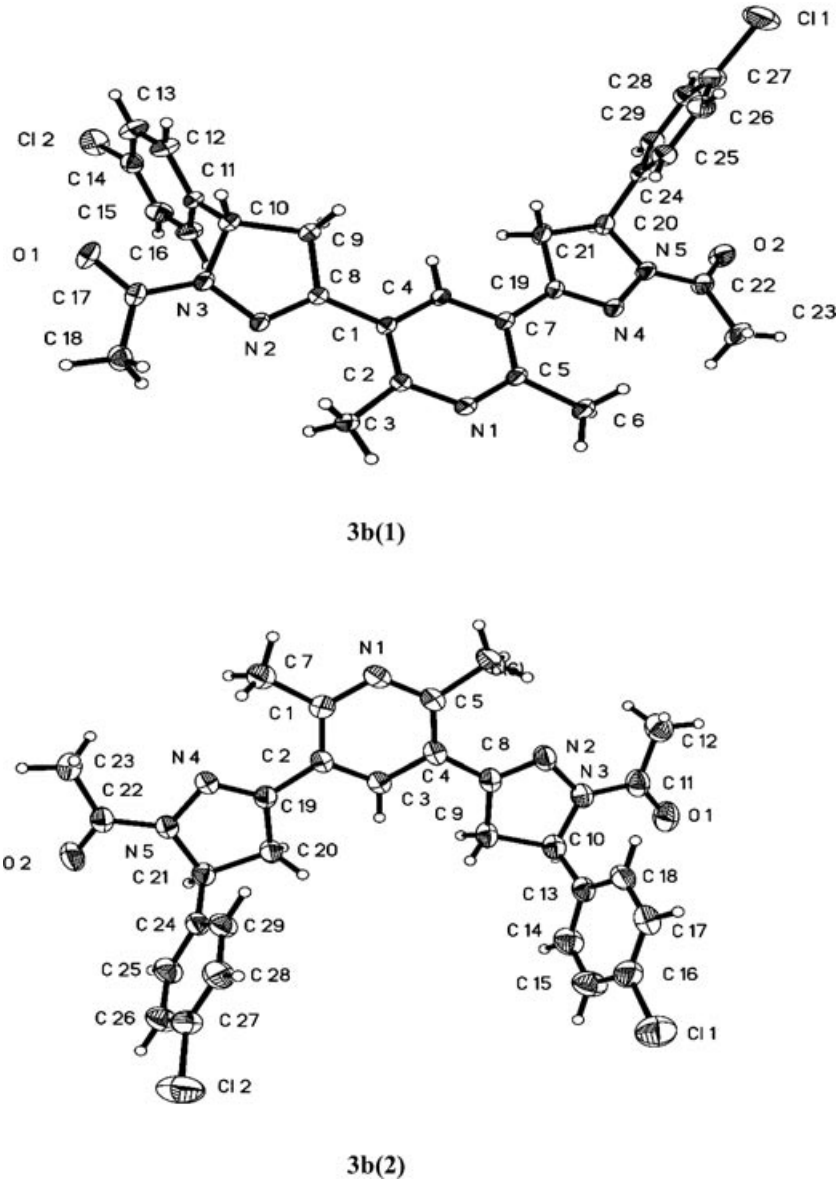

FIGURE 1 X-ray crystal structures of **3b**(**1**) and **3b**(**2**).

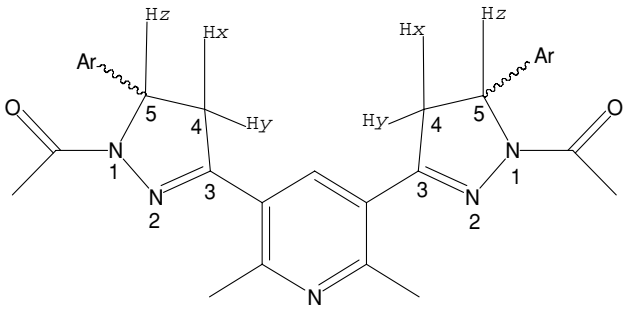

FIGURE 2 Structure of compound **3**, indicating the H*x*, H*y* and H*z* respectively.

that pyridine ring and two 1-acetyl pyrazole rings adopted the coplanar structure in unit cell.

The characteristic features of ^{1}H NMR spectra of **3**(**1**) were the appearance of three-group doublet–doublet peaks at $\delta = 3.16$, 3.76, and 5.55 ppm, respectively, with $Jxz = 5.0$ Hz, $Jyz = 12.0$ Hz, and $Jxy = 17.5$ Hz for the H*x*, H*y*, and H*z* protons (Fig. 2). The ^{1}H NMR spectra of **3**(**2**) had the similar patterns compared with that of **3**(**1**). Moreover, the different values of chemical shifts were less than 15 ppm for the corresponding protons of **3b**(**1**) and **3b**(**2**), respectively.

To expand the utilization of **1** for synthesizing diverse heterocycles, we investigated that **1** reacted with 2 equiv of 2-arylidenemalononitrile in the presence of excess of KOH in MeOH. It was hoped that 2,2′-(2,6-dimethyl-3,5-pyridinyl)bisbipyridine-5-carbonitriles could be obtained. After stirring the mixture at room temperature for 20 h, a completion reaction was observed by TLC analysis. To our surprise, general workup afforded 5′-acetyl[2,3′-bipyridine]-5-carbonitrile derivatives **4** exclusively in fair to moderate yields, no 2,2′-(2,6-dimethyl-3,5-pyridinyl)bisbipyridine-5-carbonitrile was detected.

To further study the structure of products related to the reaction conditions, we screened various reaction conditions by varying molar ratio, base, reaction temperature, and solvents. First, we examined the amount of 2-arylidenemalononitrile affecting the formation of products. The reactions gave the same result, although the amount of 2-arylidenemalononitrile was increased up to 4 equiv. Second, in the presence of excess of MeOK, a variety of solvents such as THF, CH_3CN, DMF, PhMe, and DCM were also screened. Finally, the reaction was performed at higher temperature up to 90°C. However, all attempts gave the same reaction results, providing 5′-acetyl[2,3′-bipyridine]-5-carbonitrile derivatives **4** as an exclusive product, without the formation of 2,2′-(2,6-dimethyl-3,5-pyridinyl)bisbipyridine-5-carbonitrile derivatives.

TABLE 2 Synthesis of 5′-Acetyl-4-aryl-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile[a]

Entry	*Ar*	*Product*	*Yield of* **4** *(%)*[b]
1	4-Cl-C_6H_4	**4a**	56
2	C_6H_5	**4b**	48
3	4-$(CH_3)_2$N-C_6H_4	**4c**	51
4	4-CH_3O-C_6H_4	**4d**	53
5	4-HO-C_6H_4	**4e**	49
6	2-furyl	**4f**	47
7	3,4-$(CH_3O)_2$-C_6H_3	**4g**	50
8	2,4-Cl_2-C_6H_3	**4h**	56

[a]Reaction conditions: **1** (1 mmol), 2-arylidenemalononitrile (1 mmol), KOH (1 mmol); solvent: MeOH/H_2O (v/v = 1:1); rt, 20 h.
[b]Isolated yield.

Under the optimal reaction conditions, we carried out the reactions with diverse 2-arylidenemalonnitrile, including 2-furylmethylenemalononitrile. The corresponding target products were successfully obtained. The reaction results are outlined in Table 2. Noticeably, the nature of the substituents had no major effect on the reaction outcome.

CONCLUSION

In conclusion, 3,5-diacetyl-2,6-dimethylpyridine, which was readily available and poorly explored, has successfully been utilized as starting material for synthesis of novel (1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazole)-substituted pyridine derivatives and polysubstituted [2,3′-bipyridine]-5-carbonitrile derivatives. Our work furnished the compound libraries of polysubstituted pyridine derivatives, as well as the methodology for synthesis of heterocycles from a versatile synthetic precursor.

EXPERIMENTAL

Melting points were measured with digital melting point apparatus (WRS-1B, Shanghai Precision & Scientific Instrument Co., Ltd.) and were uncorrected. All NMR spectra were obtained in $CDCl_3$ DMSO-d_6 on Bruker AM-500 instruments with Me_4Si as the internal standards. FTIR spectra were obtained with a Nicolet AVATAR-370 spectrophotometer. Mass spectrum was determined with Finnigan GC-MS 4021. Elemental analyses were performed using a Vario ELIII Analyzer. X-ray crystal structure data were collected on a Bruck SMART CCD area detector diffractometer using graphite-monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å). Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm silica gel plates visualized with UV light.

General Procedure for the Synthesis of (2E,2′E)-1,1′-(2,6-Dimethyl-3,5-pyridinediyl)bis[3-aryl-2-propen-1-one] Derivatives **2a–h** *and 3,5-Bis(1-acetyl-5-ary-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridines* **3a–h**

Synthesis of **2g, h**. About 5 mmol of **1** and 10 mmol of aryl aldehyde were dissolved in 5 mL of MeOH/H_2O (v/v = 5:1) and 10 mmol of KOH was added [14]. The mixture was stirred for 6 h at 0°C. The resulting solid was filtered, washed with water, and recrystallized from 95% ethanol to obtain the pure product.

Synthesis of **2a–f**. About 5 mmol of **1** and 10 mmol of aryl aldehyde were dissolved in 5 mL of acetic acid and 5 mL condensed sulfuric acid was added. The mixture was stirred for 6 h at 100°C, allowed to cool at room temperature, and poured into ice water and then neutralized with 10% sodium hydroxide solution. The resulting solid was filtered, washed with water, and recrystallized from 95% ethanol to obtain the pure product.

*(2E,2′E)-1,1′-(2,6-Dimethyl-3,5-pyridinediyl)bis-[3-(2-chlorophenyl)-2-propen-1-one] (**2d**).* White solid, mp: 178–180°C. Yield: 84%. IR (KBr, cm^{-1}): 3067, 1659, 1599, 764. ^1H NMR ($CDCl_3$, 500 MHz): 2.75 (s, 6H, CH_3), 7.10 (s, 1H, CH=CH), 7.11 (s, 1H, CH=CH), 7.30–7.71 (m, 8H, Ar-H), 7.95 (s, 1H, CH=CH), 7.98 (s, 1H, CH=CH), 7.99 (s, 1H, py-H). ESI-MS *m/z* (434.4 M^+). Anal. Calcd for $C_{25}H_{19}Cl_2NO_2$: C, 68.82; H, 4.39; N, 3.21. Found: C, 68.69; H, 4.18; N, 3.36.

*(2E,2′E)-1,1′-(2,6-Dimethyl-3,5-pyridinediyl)bis-[3-(2,4-dichloropheny)-2-propen-1-one] (**2e**).* White solid, mp: 197–199°C. Yield: 92%. IR (KBr, cm^{-1}): 3057, 1605, 1584, 826, 777. ^1H NMR ($CDCl_3$, 500 MHz): 2.75 (s, 6H, CH_3), 7.10 (s, 1H, CH=CH), 7.11 (s, 1H, CH=CH), 7.30–7.64 (m, 6H, Ar-H), 7.87 (s, 1H, CH=CH), 7.90 (s, 1H, CH=CH), 7.98 (s, 1H, py-H). ESI-MS *m/z* (503.3, M^+). Anal. Calcd for $C_{25}H_{17}Cl_4NO_2$: C, 59.43; H, 3.39; N, 2.77. Found: C, 59.61; H, 3.16; N, 2.69.

*(2E,2′E)-1,1′-(2,6-Dimethyl-3,5-pyridinediyl)bis-[3-(2-fluorophenyl)-2-propen-1-one] (**2f**).* White solid, mp: 161–163°C. Yield: 89%. IR (KBr, cm^{-1}): 3068, 1651, 1601, 749. ^1H NMR ($CDCl_3$, 500 MHz): 2.74 (s, 6H, CH_3), 7.10–7.22 (m, 4H, Ar-H), 7.22 (s, 1H, CH=CH), 7.23 (s, 1H, CH=CH), 7.39–7.62 (m, 4H, Ar-H), 7.67 (s, 1H, CH=CH), 7.70 (s, 1H, CH=CH), 7.97 (s, 1H, py-H). ESI-MS *m/z* (401.5, M^+). Anal. Calcd for $C_{25}H_{19}F_2NO_2$: C, 74.43; H, 4.75; N, 3.47. Found: C, 74.59; H, 4.68; N, 3.39.

Synthesis of 3,5-Bis(1-acetyl-5-ary-4,5-dihydro-1H-pyrazol-3-yl)-2,6-dimethylpyridine **3a–h**

About 1 mmol of **2** and 2 mmol of 85% hydrazine hydrate solution were dissolved in 5 mL of acetic acid. The mixture was refluxed for 8 h, allowed to cool at room temperature, and poured into ice water and then neutralized with 10% sodium hydroxide solution. The resulting solid was filtered, washed with water, dried, and purified by column chromatography on silica gel using ethyl acetate/dichloromethane (v/v = 1/2) as eluent.

*3,5-Bis(1-acetyl-4,5-dihydro-5-phenyl-1H-pyrazol-3-yl)-2,6-dimethylpyridine (**3a**).* **3a**(**1**): White solid, mp: 269–271°C. IR (KBr, cm^{-1}): 1677, 1594, 1432, 1404, 699. ^1H NMR ($CDCl_3$, 500 MHz): 2.42 (s, 6H, CH_3), 2.92 (s, 6H, CH_3C=O), 3.16 (dd, J = 5.0, 17.5Hz, 2H, H-*x*), 3.76 (dd, 2H, J = 12.0, 17.5 Hz, H-*y*), 5.55 (dd, 2H, J = 5.0, 12.0 Hz, H-*z*), 7.54 (s, 1H, py-H), 7.19–7.35 (m, 10H, Ar-H). ESI-MS *m/z* (480.2, M^+). Anal. Calcd for $C_{29}H_{29}N_5O_2$: C, 72.63; H, 6.10; N, 14.60. Found: C, 72.27; H, 6.08; N, 14.39.

3a(**2**): White solid, mp: 264–266°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.42 (s, 6H, CH_3), 2.92 (s, 6H, CH_3C = O), 3.15 (dd, J = 5.0, 17.5 Hz, 2H, H-*x*), 3.77 (dd, 2H, J = 12.0, 17.5 Hz, H-*y*), 5.56 (dd, 2H, J = 5.0, 12.0 Hz, H-*z*), 5.55–5.58 (s, 1H, py-H), 7.18–7.33 (m, 10H, Ar-H). EI-MS *m/z* (100%): 479 (M^+, 96), 438 (32), 439 (100), 422 (17), 395 (54), 380 (16). Anal. Calcd for $C_{29}H_{29}N_5O_2$: C, 72.63; H, 6.10; N, 14.60. Found: C, 72.31; H, 6.05; N, 14.42.

*3,5-Bis[1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3b**).* **3b**(**1**): White solid, mp: 261–268°C. IR (KBr, cm^{-1}): 1652, 1595, 1492, 1406, 1364, 822. ^1H NMR ($CDCl_3$, 500 MHz): 2.41 (s, 6H, CH_3), 2.91 (s, 6H, CH_3C=O), 3.13 (dd, J = 5.0, 17.5 Hz, 2H, H-*x*), 3.77 (dd, 2H, J = 12.0, 17.5 Hz, H-*y*), 5.52 (dd, 2H, J = 5.0, 12.0 Hz, H-*z*), 7.53 (s, 1H, py-H), 7.13–7.31 (m, 10H, Ar-H). ESI-MS *m/z* (548.2, M^+). Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.49; H, 4.95; N, 12.65.

3b(**2**): White solid, mp: 274–276°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.41 (s, 6 H, CH_3), 2.93 (s, 6H, CH_3C=O), 3.12 (dd, J = 5.0, 17.5 Hz, 2H, H-*x*), 3.78 (dd, 2H, J = 12.0, 17.5 Hz, H-*y*), 5.53 (dd, 2H, J = 5.0, 12.0 Hz, H-*z*), 7.53 (s, 1H, py-H), 7.13–7.30 (m, 10H, Ar-H). EI-MS *m/z* (100%): 547 (M^+, 79), 507 (69), 505 (100), 463 (58), 448 (21), 324 (17), 140 (18), 125 (24).

Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.41; H, 4.93; N, 12.69.

*3,5-Bis[1-acetyl-5-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3c**).* **3c**(**1**): White solid, mp: 223–225°C. IR (KBr, cm^{-1}): 1666, 1593, 1438, 1406, 1364, 789. ^1H NMR ($CDCl_3$, 500 MHz): 2.42 (s, 6H, CH_3), 2.91 (s, 6H, $CH_3C{=}O$), 3.14 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.78 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.52 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.53 (s, 1H, py-H), 7.09–7.29 (m, 10H, Ar-H). ESI-MS *m/z* (548.2, M^+). Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.54; H, 4.95; N, 12.68.

3c(**2**): White solid, mp: 239–241°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.42 (s, 6H, CH_3), 2.92 (s, 6H, $CH_3C{=}O$), 3.14 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.78 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.52 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.52 (s, 1H, py-H), 7.08–7.27 (m, 10H, Ar-H). EI-MS *m/z* (100%): 547 (M^+, 71), 507 (46), 505 (100), 463 (55), 352 (24), 140 (20), 125 (23), 111 (22). Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.56; H, 4.92; N, 12.70.

*3,5-Bis[1-acetyl-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3d**).* **3d**(**1**): White solid, mp: 268–270°C. IR (KBr, cm^{-1}): 1656, 1593, 1475, 1406, 363, 756. ^1H NMR ($CDCl_3$, 500 MHz): 2.46 (s, 6H, CH_3), 2.89 (s, 6H, $CH_3C{=}O$), 3.06 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.85 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.86 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.48 (s, 1H, py-H), 7.05–7.47 (m, 10H, Ar-H). ESI-MS *m/z* (548.2, M^+). Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.24; H, 4.93; N, 12.58.

3d(**2**): White solid, mp: 265–267°C. ^1H NMR ($CDCl_3$, 500MHz): 2.46 (s, 6H, CH_3), 2.89 (s, 6H, $CH_3C{=}O$), 3.05 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.86 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.87 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.48 (s, 1H, py-H), 7.04–7.40 (m, 10H, Ar-H). EI-MS *m/z* (100%): 547 (M^+, 84), 507 (75), 505 (100), 470 (26), 465 (42), 463(74), 327 (27), 146 (25), 140 (25), 125 (36). Anal. Calcd for $C_{29}H_{27}Cl_2N_5O_2$: C, 63.51; H, 4.96; N, 12.77. Found: C, 63.36; H, 4.91; N, 12.63.

*3,5-Bis[1-acetyl-5-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3e**).* **3e**(**1**): White solid, mp: 279–281°C. IR (KBr, cm^{-1}): 1654, 1592, 1472, 1405, 1364, 869, 819. ^1H NMR (DMSO-d_6, 500 MHz): 2.33 (s, 6H, CH_3), 2.82 (s, 6H, $CH_3C{=}O$), 3.27 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.96 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.67 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.78 (s, 1H, py-H), 7.12–7.67 (m, 10H, Ar-H). ESI-MS *m/z* (618.0, M^+). Anal. Calcd for $C_{29}H_{25}Cl_4N_5O_2$: C, 56.42; H, 4.08; N, 11.34. Found: C, 56.22; H, 4.17; N, 11.12.

3e(**2**): White solid, mp: 308–310°C. ^1H NMR (DMSO-d_6, 500 MHz): 2.33 (s, 6H, CH_3), 2.83 (s, 6H, $CH_3C{=}O$), 3.29 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.94 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.67 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.76 (s, 1H, py-H), 7.10–7.64 (m, 10H, Ar-H). EI-MS *m/z* (100%): 617 (M^+, 75), 615 (55), 577 (57), 575 (100), 573 (76), 535 (33), 531 (49), 172 (35). Anal. Calcd for $C_{29}H_{25}Cl_4N_5O_2$: C, 56.42; H, 4.08; N, 11.34. Found: C, 56.36; H, 4.13; N, 11.28.

*3,5-Bis[1-acetyl-4,5-dihydro-5-(2-fluorophenyl)-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3f**).* **3f**(**1**): Yellow solid, mp: 217–219°C. IR (KBr, cm^{-1}): 1661, 1590, 1492, 1404, 1362, 757. ^1H NMR ($CDCl_3$, 500 MHz): 2.43 (s, 6H, CH_3), 2.90 (s, 6H, $CH_3C{=}O$), 3.16 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.79 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.74 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.54 (s, 1H, py-H), 7.04–7.28 (m, 10H, Ar-H). ESI-MS *m/z* (516.2, M^+). Anal. Calcd for $C_{29}H_{27}F_2N_5O_2$: C, 67.56; H, 5.28; N, 13.58. Found: C, 67.49; H, 5.19; N, 13.27.

3f(**2**): Yellow solid, mp: 242–244°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.45 (s, 6H, CH_3), 2.93 (s, 6H, $CH_3C{=}O$), 3.18 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.83 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.78 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.55 (s, 1H, py-H), 7.05–7.26 (m, 10H, Ar-H). EI-MS *m/z* (100%): 515 (M^+, 95), 474 (31), 473 (100), 432 (18), 431 (64), 311 (20), 109 (21). Anal. Calcd for $C_{29}H_{27}F_2N_5O_2$: C, 67.56; H, 5.28; N, 13.58. Found: C, 67.53; H, 5.21; N, 13.42.

^{19}F NMR ($CDCl_3$, 470 MHz): **3f**(**1**) δ: −117.6–−117.7 (m, F); **3f**(**2**) δ: −117.6—117.7 (m, F).

*3,5-Bis[1-acetyl-4,5-dihydro-5-(4-methoxyphenyl)-1H-pyrazol-3-yl]-2,6-dimethylpyridine (**3g**).* **3g**(**1**): White solid, mp: 230–232°C. IR (KBr, cm^{-1}): 1660, 1513, 1405, 1366, 870, 829. ^1H NMR ($CDCl_3$, 500 MHz): 2.40 (s, 6H, CH_3), 2.91 (s, 6H, $CH_3C{=}O$), 3.15 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.73 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 3.77 (s, 6H, OCH_3), 5.51 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.56 (s, 1H, py-H), 6.84–7.15 (m, 10H, Ar-H). ESI-MS *m/z* (540.2, M^+). Anal. Calcd for $C_{31}H_{33}N_5O_4$: C, 69.00; H, 6.16; N, 12.98. Found: C, 68.76; H, 6.55; N, 12.69.

3g(**2**): White solid, mp: 213–215°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.40 (s, 6H, CH_3), 2.91 (s, 6H, $CH_3C{=}O$), 3.15 (dd, $J = 12.0$, 17.5 Hz, 2H, H-*x*), 3.75 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*y*), 3.77 (s, 6H, OCH_3), 5.51 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.55 (s, 1H, py-H), 6.83–7.13 (m, 10H, Ar-H). EI-MS *m/z* (100%): 539 (M^+, 100), 497 (60), 482 (33), 440 (25), 349 (25), 191 (40), 176 (38), 149 (27), 176 (38). Anal. Calcd for

$C_{31}H_{33}N_5O_4$: C, 69.00; H, 6.16; N, 12.98. Found: C, 68.82; H, 6.39; N, 12.85.

*3,5-Bis[1-acetyl-4,5-dihydro-5-(4-nitrophenyl)-1H-pyrazol-3-yl]-2,6-dimethylpyridine (***3h***).* **3h**(**1**): Yellow solid, mp: 280–282°C. IR (KBr, cm^{-1}): 1670, 1596, 1518, 1405, 1348, 853. ^1H NMR (DMSO-d_6, 500 MHz): 2.32 (s, 6H, CH_3), 2.84 (s, 6H, $CH_3C{=}O$), 3.35 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.93 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.63 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.80 (s, 1H, py-H), 7.48–7.50 (d, 4H, Ar-H), 8.19–8.21 (d, 4H, Ar-H). ESI-MS *m*/*z* (570.2, M^+). Anal. Calcd for $C_{29}H_{25}N_7O_6$: C, 61.37; H, 4.44; N, 17.28. Found: C, 60.97; H, 4.78; N, 16.92.

3h(**2**): Yellow solid, mp: 265–267°C. ^1H NMR (DMSO-d_6, 500 MHz): 2.32 (s, 6H, CH_3), 2.85 (s, 6H, $CH_3C{=}O$), 3.40 (dd, $J = 5.0$, 17.5 Hz, 2H, H-*x*), 3.90 (dd, 2H, $J = 12.0$, 17.5 Hz, H-*y*), 5.63 (dd, 2H, $J = 5.0$, 12.0 Hz, H-*z*), 7.79 (s, 1H, py-H), 7.46–7.48 (d, 4H, Ar-H), 8.16–8.18 (d, 4H, Ar-H). EI-MS *m*/*z* (100%): 569 (M^+, 37), 528 (33), 527 (100), 486 (25), 485 (79), 363 (28), 321 (64), 164 (33). Anal. Calcd for $C_{29}H_{25}N_7O_6$: C, 61.37; H, 4.44; N, 17.28. Found: C, 61.19; H, 4.56; N, 16.99

General Procedure for the Synthesis of 5′-Acetyl-4-aryl-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitriles **4a–h**

About 2 mmol of **1** was dissolved in 5 mL of MeOH, 2.2 mmol of KOH was dissolved in 1 mL of water, and taken in a 25 mL round bottom flask. Then, added 2 mmol 2-arylidenemalononitrile slowly. The mixture was stirred at room temperature for 20 h, poured into cold water, and then neutralized with acetic acid. The solid separated was filtered, washed with water, and recrystallized from EtOH/THF (v/v = 2/1) to obtain the pure product.

*5′-Acetyl-4-(4-chlorophenyl)-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4a***).* White solid, mp: 239–241°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.62 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.14 (s, 3H, CH_3O), 7.17 (s, 1H, pyridine-5-H), 7.52–7.60 (m, 4H, Ar-H), 8.09 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2224, 1690, 1593, 1452, 1365, 1260, 1004, 832. ESI-MS *m*/*z* (391.0, M^+). Anal. Calcd for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.22; H, 4.77; N 10.35.

*5′-Acetyl-6-methoxy-4-phenyl-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4b***).* White solid, mp: 172–174°C. ^1H NMR($CDCl_3$, 500 MHz): 2.62 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.18 (s, 3H, CH_3O), 7.21 (s, 1H, pyridine-5-H), 7.54–7.66 (m, 5H, Ar-H), 8.12(s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2226, 1688, 1584, 1549, 1459, 1369, 762, 695. ESI-MS *m*/*z* (357.2, M^+). Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.73; H, 5.43; N, 11.66.

*5′-Acetyl-6-methoxy-4-(4-N,N-dimethylphenyl)-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4c***).* Yellow solid, mp: 197–199°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.62 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.05 [s, 6H, $N(CH_3)_2$], 4.11 (s, 3H, CH_3O), 7.17 (s, 1H, pyridine-5-H), 6.79–7.64 (m, 4H, Ar-H), 8.10 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2218, 1682, 1580, 1526, 1451, 1365, 828. ESI-MS *m*/*z* (400.2, M^+). Anal. Calcd for $C_{24}H_{24}N_4O_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.63; H, 6.12; N, 13.75.

*5′-Acetyl-6-methoxy-4-(4-methoxyphenyl)-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4d***).* White solid, mp: 199–201°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.62 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.88 (s, 3H, Ar-OCH_3), 4.13 (s, 3H, CH_3O), 7.18 (s, 1H, pyridine-5-H), 7.05–7.64 (m, 4H, Ar-H), 8.10 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2226, 1687, 1584, 1144, 1516, 1452, 830. ESI-MS *m*/*z* (387.2, M^+). Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.21; H, 5.47; N, 10.62.

*5′-Acetyl-4-(4-hydroxylphenyl)-6-methoxy-2′,6′-dimethyl[2,3′-*bipyridine*]-5-carbonitrile (***4e***).* Yellow solid, mp: 260–262°C. ^1H NMR (DMSO-d_6, 500 MHz): 2.62 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.06 (s, 3H, CH_3O), 7.56 (s, 1H, pyridine-5-H), 6.95–7.65 (m, 4H, Ar-H), 8.39 (s, 1H, pyridine-4-H), 10.12 (s, 1H, OH). IR (KBr, cm^{-1}): 2220, 1684, 1591, 1551, 1452, 1361, 848. ESI-MS *m*/*z* (373.2, M^+). Anal. Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.43; H, 5.18; N, 10.90.

*5′-Acetyl-4-furanyl-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4f***).* White solid, mp: 227–229°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.64 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.11 (s, 3H, CH_3O), 7.56 (s, 1H, pyridine-5-H), 6.69 (s, 1H, furan-H), 7.65–7.68 (m, 2H, furan-H), 8.11 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2224, 1688, 1592, 1552, 1457, 1359, 767. ESI-MS *m*/*z* (347.1, M^+). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 68.77; H, 4.99; N, 12.10.

*5′-Acetyl-4-(3,4-dimethoxyphenyl)-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4g***).* White solid, mp: 169–171°C. ^1H NMR (DMSO-d_6, 500 MHz): 2.63 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.84 (s, 3H, Ar-OCH_3), 3.85 (s,

3H, Ar-OCH_3), 4.08 (s, 3H, CH_3O), 7.16 (s, 1H, pyridine-5-H), 7.17–7.64 (m, 3H, Ar-H), 8.39 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2220, 1685, 1584, 1547, 1517, 1453, 767, 668. ESI-MS *m/z* (417.2, M^+). Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.84; H, 5.62; N, 10.14.

*5′-Acetyl-4-(2,4-dichlorophenyl)-6-methoxy-2′,6′-dimethyl[2,3′-bipyridine]-5-carbonitrile (***4h***).* White solid, mp: 141–143°C. ^1H NMR ($CDCl_3$, 500 MHz): 2.62 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.16 (s, 3H, CH_3O), 7.15 (s, 1H, pyridine-5-H), 7.35–7.60 (m, 3H, Ar-H), 8.12 (s, 1H, pyridine-4-H). IR (KBr, cm^{-1}): 2223, 1689, 1589, 1559, 1479, 1366, 998, 829. ESI-MS *m/z* (425.1, M^+). Anal. Calcd for $C_{22}H_{17}Cl_2N_3O_2$: C, 61.98; H, 4.02; N, 9.86. Found: C, 62.32; H, 4.28; N, 9.63.

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