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# Efficient di-bromination of 5-pyrazolones and 5-hydroxypyrazoles by *N*-bromobenzamide

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ABSTRACT

An efficient and convenient method for the bromination of pyrazolones and 5-hydroxypyrazoles was developed by using *N*-bromobenzamide in THF at room temperature. This new method provided di-bromimated pyrazolones in excellent yields (≥90%).



## 1. Introduction

Pyrazolones[1] and pyrazoles[2] attract attentions due to their wide range of pharmacological proprieties.[3–7] Some halogenated pyrazolones also displayed bioactivities, examples include 4,4-dichloro-5-pyrazolone derivatives as a potent catalytic inhibitor of human telomerase[8] and 4,4-dibromo-5-pyrazolone as fungicide against *Helminthosporium oryzae*,[9] α-glucosidase inhibitors, and for treatment of tumor metastasis, AIDS, diabetes, hyperlipidemia, autoimmune disease, allergy, rejection in organ transplant, etc.[10] Pyrazolones and pyrazoles are key starting materials for the synthesis of commercial aryl/heteroaropyrazolone dye.[11,12] Brominated and chlorinated pyrazolones are also useful synthetic intermediates for synthesis of diazo-dyes,[13] fused-[14] and spiro-heterocyclic compounds.[15]

Traditional methods for the synthesis of brominated pyrazolones contain the use of $Br_2$ in acetic acid,[12] however, the harsher conditions require manipulations with care. Ahmed et al. have treated the pyrazolones with *N*-bromosuccinimide (NBS) to perform the photochemical bromination.[16] Since the reaction also provided the mono-substituted and coupling by-products, the desired dibromopyrazolines were obtained in low yields.[16] Commercially available *N*-bromobenzamide has been also reported as a mild and effective brominating agent with unsaturated alkenes.[17] They were also demonstrated to act as an oxidant agent[18,19] and nitrogen source in the asymmetric aminohydroxylation process.[19] Herein, we report the use of *N*-bromobenzamide as a safe and efficient bromination agent for pyrazolones and 5-hydroxypyrazoles. The newly developed method provided the corresponding di-brominated pyrazolones in excellent yields (≥90%). The reaction proceeded smoothly at room temperature with easy manipulation. Comparing *N*-bromobenzamide and *N*-bromosuccinimide (NBS) as the brominating agents toward pyrazolone reactants, we found that *N*-bromobenzamide can provide more efficient reactivity than *N*-bromosuccinimide (NBS).

## 2. Result and discussion

We first prepared 5-pyrazolone derivatives as the starting materials by tandem condensation and thermal cyclization.[20] α-Keto esters **1** were heated at reflux with equal equivalent of arylylhydrazines **2a**–**2h** possessing various substituents including *m*-Me, *p*-OMe, *p*-$NO_2$ and 2,4,6,-trichloro in AcOH for 4 h. The corresponding 5-pyrazolones (keto form) were obtained in good to excellent yields (75–95%, see Scheme 1, Chart 1, and Table 1).[20] When the reaction was performed under microwave radiation, the reaction time was decreased to 10 min and the excellent yields of the products were also obtained. Use of hydrazine, and pyridyl and

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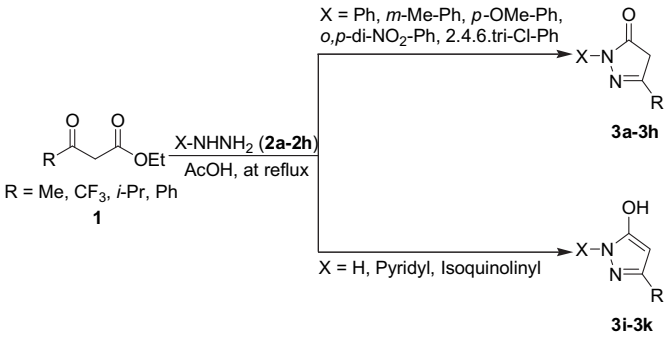
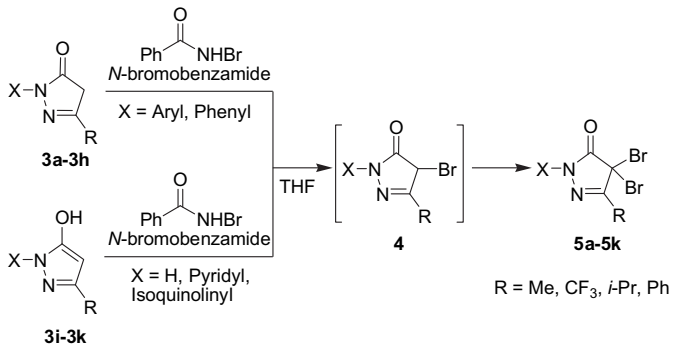



**Scheme 1.**




**Scheme 2.**

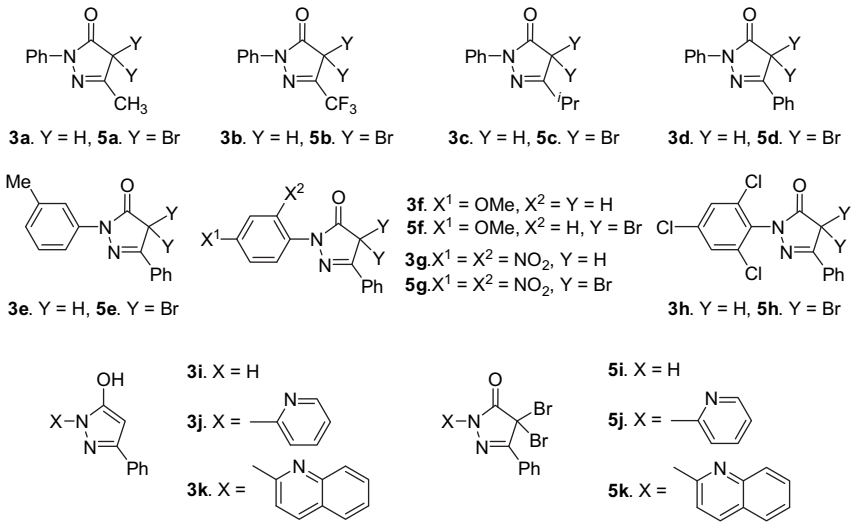



**Chart 1.**

**Table 1**
The results of tandem thermal condensation/cyclization[a]

| Hydrazines (**2a–2h**) | | 5-Pyrazolones (**3a–3h**) or 5-hydroxypyrazoles (**3i–3k**) | | |
|---|---|---|---|---|
| Substrates | X | Compounds | R | Yields (%) |
| **2a** | Ph | **3a** | Me | 91 |
| **2a** | Ph | **3b** | $CF_3$ | 75 |
| **2a** | Ph | **3c** | *i*-Pr | 95 |
| **2a** | Ph | **3d** | Ph | 94 |
| **2b** | *m*-Me-Ph | **3e** | Ph | 88 |
| **2c** | *p*-OMe-Ph | **3f** | Ph | 90 |
| **2d** | *o*,*p*-di-$NO_2$-Ph | **3g** | Ph | 82 |
| **2e** | 2,4,6,-Trichloro-Ph | **3h** | Ph | 85 |
| **2f** | H | **3i** | Ph | 96 |
| **2g** | Pyridyl | **3j** | Ph | 88 |
| **2h** | Isoquinolinyl | **3k** | Ph | 86 |

[a] The tandem thermal condensation and cyclization in AcOH at reflux for 4 h.

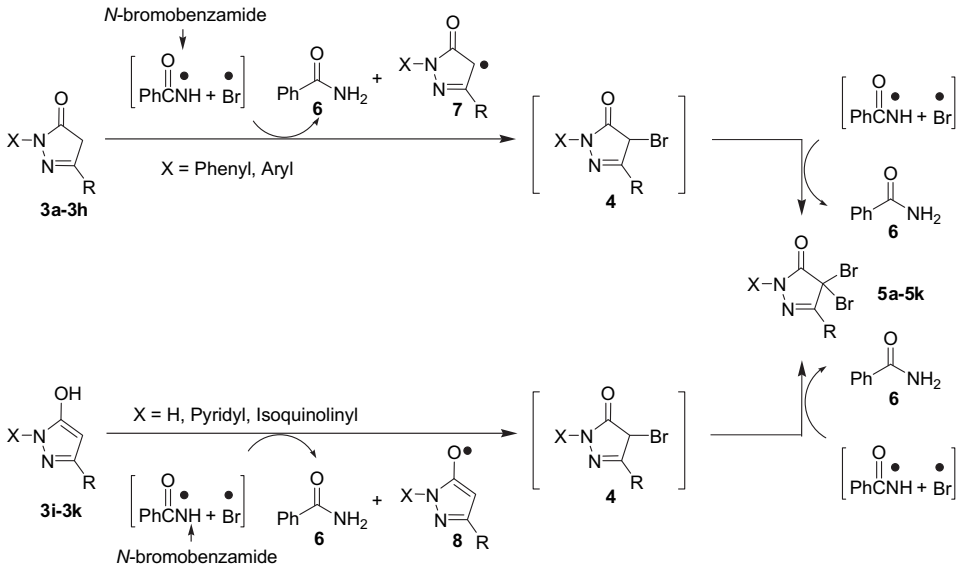
isoquinolinyl hydrazines as the starting material provided the corresponding 5-hydroxypyrazoles **3i–3k** (enol form) in 86–88% yields (see Scheme 1, Chart 1, and Table 1). The experiment results were consistent with the reported literature.[21,22] When acetyl and isonicotinoyl hydrazines reacted with ethyl benzoylacetate (**1**), only 3-phenyl-1*H*-pyrazol-5-ol (**3i**) was obtained due to the instability of the amide bond (–(C═O)–N–) in acidic condition.

The *N*-bromobenzamide was allowed to react with pyrazolones for the investigation of its feasibility of di-bromination. Treatment of 5-pyrazolone **3a** with *N*-bromobenzamide in THF solution at room temperature for 1 h gave 4,4-dibromo-5-pyrazolone **5a** in 96% yield (see Chart 1 and Scheme 2). Compound **5a** was fully characterized by spectroscopic method and consistent with the reported data.[13,16] By employing same conditions as shown in Scheme 2, 5-pyrazolones **3b–3h** bearing *N*-substituted phenyl group including *m*-Me, *p*-OMe, *o*,*p*-di-$NO_2$-Ph, and 2,4,6-trichloro was successfully di-brominated to the corresponding products **5b–5h** in ≥91% yields (see Table 2). This reaction was also applicable to the 5-hydroxypyrazole (enol form) bearing *N*-substituted group, such as H, pyridyl, and isoquinolinyl (compounds **3i–3k**). The desired di-brominated compounds **5i–5k** were obtained in 90–93% yields. For example, compound **5j** possessed characterization absorptions at $\delta$ 42.4 ppm for *gem*-dibromomethylene carbon [O═C–$^{13}$C(Br)$_2$] in pyrazolone ring and IR absorptions at 1744 cm$^{-1}$ for the stretching of the –C═O group. When 2-pyrrolidinone and γ-butyrolactone were allowed to react with *N*-bromobenzamide,

**Table 2**
The results of bromination by using *N*-bromobenzamide

| 5-Pyrazolones (**3a–3h**) or 5-hydroxypyrazoles (**3i–3k**) | | | Bromination[a] (**5a–5k**) | |
|---|---|---|---|---|
| Compounds | X | R | Products | Yields (%) |
| **3a** | Ph | Me | **5a** | 96 |
| **3b** | Ph | $CF_3$ | **5b** | 93 |
| **3c** | Ph | *i*-Pr | **5c** | 95 |
| **3d** | Ph | Ph | **5d** | 98 |
| **3e** | *m*-Me-Ph | Ph | **5e** | 96 |
| **3f** | *p*-OMe-Ph | Ph | **5f** | 92 |
| **3g** | *o*,*p*-di-$NO_2$-Ph | Ph | **5g** | 91 |
| **3h** | 2,4,6,-Trichloro-Ph | Ph | **5h** | 96 |
| **3i** | H | Ph | **5i** | 93 |
| **3j** | Pyridyl | Ph | **5j** | 93 |
| **3k** | Isoquinolinyl | Ph | **5k** | 90 |

[a] The di-bromination of compounds **3i–3k** with *N*-bromobenzamide in THF solution at room temperature for 1 h.




**Scheme 3.**

the reaction did not give the desired products either at room temperature or at reflux.

We proposed a plausible mechanism for the bromination of 5-pyrazolones by use of *N*-bromobenzamide (see Scheme 3). *N*-Bromobenzamide first underwent homolytic cleavage to form two radical species (PhCONH· and Br·) by photolysis in THF at room temperature.[17a] The PhCONH· radical quickly trapped a hydrogen from the α-position of pyrazolones or from –OH group of 5-hydroxypyrazoles to generate benzamide **6** and the corresponding radical intermediate **7** or **8**.[17c] Benzamide **6** was isolated by column chromatography and identified by $^{1}H$ and $^{13}C$ NMR spectroscopic methods.[17c] The resultant α-radical of 5-pyrazolone **7** or *O*-radical of 5-hydroxypyrazole **8** was formed and reacted with Br· to give the mono-brominated pyrazolone **4**. In the presence of excess *N*-bromobenzamide, the reaction proceeded to convert pyrazolones **4** to the final di-brominated products **5a**–**5k**. For understanding the reaction mechanism, we added dihydroquinone to the reaction mixture. The reaction gave benzamide **6** and quinone without the formation of bromination adduct. We believed that the reaction favored the radical-type mechanism since the two radical species PhCONH· and Br· would be quenched by dihydroquinone. As a result, no bromination product was found.

In conclusion, we have successfully developed a brominating method by using *N*-bromobenzamide to convert pyrazolone and 5-hydroxypyrazole to the corresponding 4,4-dibromo-pyrazolones in excellent yields (≥90%). We considered the bromination procedure was a safe and efficient method in the large-scale for the preparation of 4,4-dibromo-pyrazolones.

## 3. Experimental section

### 3.1. General procedure

All chemicals were reagent grade and used as purchased unless otherwise noted. All reactions were carried out under nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from Mallinckrodt Chemical Co. The following compounds were purchased from Acros Chemical Co: *m*-tolylhydrazine hydrochloride, *tert*-butyl acetoacetate, ethyl isobutylacetate, phenylhydrazine, 4-methoxyphenylhydrazine hydrochloride, and 2,4-dinitrophenyl hydrazine. 2,4,6-Trichlorophenyl hydrazine, 2-hydrazinopyridine, and isonicotinic acid hydrazide were purchased from TCI Chemical Co. Ethyl trifluoroacetoacetate and *tert*-butyl acetoacetate were purchased from Alfa Chemical Co. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 $cm^{-1}$ absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$, $CH_3OD$, and DMSO-$d_6$ as the solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by use of $CDCl_3$, $CH_3OD$, and DMSO-$d_6$ as the solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet ($\delta$ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

### 3.2. Standard procedure for the condensation–cyclization reaction to prepare pyrazolones 3a–3h and 5-hydroxypyrazoles 3i–3k

To a neat solution containing 1,3-ketoester (**1**, 1.0 equiv) and hydrazines (**2a**–**2h**, 1.1 equiv) was added glacial acetic acid (2.0 mL). The reaction mixture was heated at reflux for 2–3 h. After the reaction was completed, the solution was diluted with $Et_2O$ (10 mL) and stirred at ice-bath for 30 min. The resultant solid was filtrated, washed with $Et_2O$ (10 mL), dried under vacuum for 12 h, and recrystallized from EtOH to give pure pyrazolones **3a**–**3h** and 5-hydroxypyrazoles **3i**–**3k** as solids in 75–96% yield.

*3.2.1. 3-Methyl-1-phenyl-2-pyrazolin-5-one (**3a**)*[22]. Mp (recrystallized from ethanol) 127–129 °C; $^{1}H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.15 (s, 3H, $CH_3$), 3.39 (s, 2H, pyrazolone-H), 7.14 (d, 1H, *J*=2.2 Hz, ArH), 7.36 (dd, 2H, *J*=7.8, 2.2 Hz, ArH), 7.81 (d, 2H, *J*=7.8 Hz, ArH); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 17.0, 43.1, 118.9 (2×CH), 125.1, 128.8 (2×CH), 137.9, 156.4, 170.6; IR (KBr) 3101 (s), 2802 (m), 1622 (s, C=O), 1584 (s, C=N), 1494 (m), 1412 (m), 1301 (s), 1220 (m), 1035 (m), 967 (m) $cm^{-1}$.

*3.2.2. 1-Phenyl-3-trifluoromethyl-2-pyrazolin-5-one (**3b**)*[22]. Mp (recrystallized from ethanol) 194–196 °C; $^{1}H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 3.71 (s, 2H, pyrazolone-H), 6.61 (s, 1H, ArH), 7.66 (d, 2H, *J*=7.8 Hz, ArH),

7.80 (d, 2H, $J$=7.6 Hz, ArH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 85.6, 122.3, 127.2, 129.1, 137.7, 140.4 (q, $_3J_{C-F}$=37.6 Hz), 153.7.

*3.2.3. 3-Isopropyl-1-phenyl-2-pyrazolin-5-one (**3c**)*[22]. Mp (recrystallized from ethanol) 101–103 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.21 (d, 6H, $J$=7.4, $CH(CH_3)_2$), 2.68–2.82 (m, 1H, $CHMe_2$), 3.37 (s, 2H, pyrazolone-H), 7.14 (t, 1H, $J$=7.4, ArH), 7.35 (dd, 2H, $J$=8.1, 7.4 Hz, ArH), 7.84 (d, 2H, $J$=8.1 Hz, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 20.1 (2×$CH_3$), 30.7, 39.8, 118.8 (2×CH), 124.9, 128.8 (2×CH), 138.2, 164.3, 170.6; IR (KBr) 3101 (s), 2802 (m), 1622 (s, C=O), 1584 (s, C=N), 1494 (m), 1412 (m), 1301 (s), 1220 (m), 1035 (m), 967 (m) cm$^{-1}$.

*3.2.4. 1,3-Diphenyl-2-pyrazolin-5-one (**3d**)*[22]. Mp (recrystallized from ethanol) 136–138 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.82 (s, 2H, pyrazolone-H), 7.24 (t, 1H, $J$=7.6, ArH), 7.44–7.53 (m, 5H, ArH), 7.82–7.86 (m, 2H, ArH), 8.01 (d, 2H, $J$=7.6 Hz, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 39.7, 119.1 (2×CH), 125.3, 126.0 (2×CH), 128.9 (2×CH), 130.7, 130.9 (2×CH), 134.8, 138.1, 154.6, 170.2; IR (KBr) 3067 (m), 1715 (s, C=O), 1601 (s, C=N), 1496 (m), 1383 (m), 1326 (m), 1172 (m), 1116 (m), 899 (m) cm$^{-1}$.

*3.2.5. 1-(3′-Methylphenyl)-3-phenyl-2-pyrazolin-5-one (**3e**).* Mp (recrystallized from ethanol) 190–192 °C; $^1$H NMR ($CD_3OD$, 200 MHz) $\delta$ 2.27 (s, 3H, $CH_3$), 3.30 (s, 2H, pyrazolone-H), 7.51 (d, 2H, $J$=7.2, ArH), 7.54–7.59 (m, 5H, ArH), 7.82 (d, 2H, $J$=7.2, ArH); $^{13}$C NMR (50 MHz, $CD_3OD$) $\delta$ 15.9, 126.3 (2×CH), 126.6, 127.2, 128.0, 128.5, 129.2 (2×CH), 131.1, 131.2, 131.5, 131.7, 136.7, 149.6, 157.4; IR (KBr) 3293 (m), 3124 (s), 1880 (m), 1537 (s, C=N), 1472 (m), 1305 (m), 1147 (m), 982 (m), 807 (m) cm$^{-1}$; Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.81; H, 5.62; N, 11.22.

*3.2.6. 1-(4′-Methoxyphenyl)-3-phenyl-2-pyrazolin-5-one (**3f**)*[11]. Mp (recrystallized from ethanol) 128–130 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.78 (s, 2H, pyrazolone-H), 3.79 (s, 3H, $CH_3$), 6.90 (d, 2H, $J$=6.8 Hz, ArH), 7.40–7.44 (m, 3H, ArH), 7.73 (d, 2H, $J$=7.2 Hz, ArH), 7.81 (d, 2H, $J$=6.8 Hz, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 39.5, 55.5, 114.0 (2×CH), 121.0 (2×CH), 125.9 (2×CH), 128.9 (2×CH), 130.6, 130.9, 131.5, 154.5, 157.2, 170.0; IR (KBr) 2927 (m), 1709 (s, C=O), 1512 (s, C=N), 1500 (m), 1248 (m), 1030 (m), 832 (m) cm$^{-1}$.

*3.2.7. 1-(2′,4′-Dinitrophenyl)-3-phenyl-2-pyrazolin-5-one (**3g**).* Mp (recrystallized from ethanol) 201–203 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.88 (s, 2H, pyrazolone-H), 7.46–7.50 (m, 3H, ArH), 7.71 (d, 2H, $J$=7.4 Hz, ArH), 8.10 (d, 1H, $J$=7.8 Hz, ArH), 8.46 (dd, 1H, $J$=7.8, 2.4 Hz, ArH), 8.74 (d, 1H, $J$=2.4 Hz, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.4, 121.2, 124.9, 126.3 (2×CH), 127.5, 129.2 (2×CH), 129.8, 131.7, 134.3, 141.9, 144.6, 157.2, 169.9; IR (KBr) 3302 (m), 2920 (m), 1738 (s, C=O), 1612 (s, C=N), 1514 (m), 1337 (m), 1132 (m), 998 (m), 840 (m) cm$^{-1}$; Anal. Calcd for $C_{15}H_{10}N_4O_5$: C, 55.22; H, 3.09; N, 17.17. Found: C, 55.18; H, 3.07; N, 17.16.

*3.2.8. 1-(2′,4′,6′-Trichlorophenyl)-3-phenyl-2-pyrazolin-5-one (**3h**).* Mp (recrystallized from ethanol) 144–146 °C; $^1$H NMR ($CD_3OD$, 200 MHz) $\delta$ 3.28 (s, 2H, pyrazolone-H), 7.34–7.43 (m, 3H, ArH), 7.68–7.72 (m, 4H, ArH); $^{13}$C NMR (50 MHz, $CD_3OD$) $\delta$ 47.1, 125.4 (2×CH), 128.4 (2×CH), 128.6 (2×CH), 129.1 (2×CH), 130.6, 132.1, 136.4, 152.8, 156.9, 171.0; IR (KBr) 3075 (m), 1732 (s, C=O), 1559 (s, C=N), 1461 (s), 1380 (m), 1157 (m), 1097 (m), 983 (m), 829 (m) cm$^{-1}$; Anal. Calcd for $C_{15}H_9Cl_3N_2O$: C, 53.05; H, 2.67; N, 8.25. Found: C, 53.08; H, 2.64; N, 8.24.

*3.2.9. 5-Hydroxy-3-phenyl-1H-pyrazole (**3i**)*[22]. Mp (recrystallized from EtOH) 235–237 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 5.88 (s, 1H, pyrazole-H), 7.24 (d, 1H, $J$=3.8 Hz, ArH), 7.34 (dd, 2H, $J$=7.4, 3.8 Hz, ArH), 7.61–7.65 (d, 2H, $J$=7.4 Hz, ArH); $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 87.3, 125.1 (2×CH), 128.2, 129.2 (2×CH), 130.9, 143.8, 161.5; IR (KBr) 3024 (m), 2920 (m), 1601 (m), 1491 (m), 1450 (m), 1069 (m), 756 (m), 698 (m) cm$^{-1}$.

*3.2.10. 5-Hydroxy-3-phenyl-1-(pyrid-2-yl)-1H-pyrazole (**3j**)*[11]. Mp (recrystallized from ethanol) 110–112 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.93 (s, 1H, pyrazole-H), 7.07–7.17 (m, 1H, ArH), 7.36–7.41 (m, 3H, ArH), 7.82–7.87 (m, 3H, ArH), 8.00 (d, 1H, $J$=7.6 Hz, ArH), 8.24 (d, 1H, $J$=7.2 Hz, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 85.7, 112.3, 120.0, 125.8 (2×CH), 128.6 (3×CH), 133.1, 140.0, 145.1, 152.6, 154.6, 157.3; IR (KBr) 3056 (m), 1624 (s, C=O), 1585 (s, C=N), 1466 (m), 1384 (m), 1310 (m), 1203 (m), 1150 (m), 1086 (m), 1027 (m), 987 (m), 942 (m) cm$^{-1}$.

*3.2.11. 5-Hydroxy-3-phenyl-1-(3-isoquinolinyl)-1H-pyrazole (**3k**).* Mp (recrystallized from ethanol) 147–149 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.98 (s, 1H, pyrazole-H), 7.38–7.53 (m, 4H, ArH), 7.71–7.90 (m, 5H, ArH), 8.12–8.31 (m, 2H, ArH); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 85.9, 112.1, 125.8, 125.9 (2×CH), 126.0, 126.5, 127.0, 128.0, 128.6 (2×CH), 131.1, 133.0, 140.2, 143.8, 152.9, 153.8, 157.9; IR (KBr), 3089 (m), 1615 (s, C=O), 1595 (s, C=N), 1492 (m), 1358 (m), 1196 (m), 1002 (m), 827 (m) cm$^{-1}$; Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.28; H, 4.57; N, 14.67.

### 3.3. Standard procedure for bromination to prepare 4,4-dibromo-5-pyrazolone derivatives 5a–5k

To a solution of pyrazolones **3a**–**3h** or 5-hydroxypyrazoles **3i**–**3k** (1.0 equiv) in THF (20 mL) was added *N*-bromobenzamide (2.1 equiv). The reaction mixture was stirred at room temperature for ~1 h. The solution was concentrated under reduced pressure and the resultant oil was re-dissolved in $CH_2Cl_2$ (50 mL). The solution was washed with $H_2O$ (20 mL×2), brine (20 mL×2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes as eluant) to give 4,4-dibromo-5-pyrazolones **5a**–**5k** as solids in 90–98% yields.

*3.3.1. 4,4-Dibromo-3-methyl-1-phenyl-2-pyrazolin-5-one (**5a**)*[13,16]. Mp (purified by column chromatography on silica gel) 80–82 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.42 (s, 3H, $CH_3$), 7.21 (d, 1H, $J$=2.6 Hz, ArH), 7.39 (dd, 2H, $J$=7.4, 2.6 Hz, ArH), 7.84 (d, 2H, $J$=7.4 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 20.0, 41.7, 118.9, 125.0, 128.8, 138.1, 159.9, 170.6; IR (KBr) 3199 (m), 2960 (m), 1706 (s, C=O), 1508 (s, C=N), 1348 (m), 1227 (m), 972 (m), 754 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 362 (M+2, 7), 360 ($M^+$, 14), 358 (M−2, 7), 281 (84), 279 (84), 265 (3), 201 (20), 200 (13), 184 (3), 171 (4), 131 (3), 105 (11), 95 (7), 92 (4), 77 (100), 65 (8), 51 (13). Anal. Calcd for $C_{10}H_8Br_2N_2O$: C, 36.18; H, 2.43; N, 8.44. Found: C, 36.22; H, 2.47; N, 8.46.

*3.3.2. 4,4-Dibromo-1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one (**5b**).* Mp (purified by column chromatography on silica gel) 119–201 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.24–7.52 (m, 3H, ArH), 7.81 (d, 2H, $J$=7.8 Hz, ArH); IR (KBr) 3391 (s), 3184 (m), 1631 (s, C=O), 1576 (s, C=N), 1404 (m), 1113 (m), 773 (m), 704 (m), 633 (m) cm$^{-1}$. Anal. Calcd for $C_{10}H_5Br_2F_3N_2O$: C, 31.12; H, 1.31; N, 7.26, Found: C, 31.32; H, 1.28; N, 7.34.

*3.3.3. 4,4-Dibromo-3-isopropyl-1-phenyl-2-pyrazolin-5-one (**5c**).* Mp (purified by column chromatography on silica gel) 77–79 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.44 (d, 6H, $J$=7.2 Hz, 2×$CH_3$), 3.06 (m, 1H, $CHMe_2$), 7.23 (d, 1H, $J$=7.9 Hz, ArH), 7.41 (dd, 2H, $J$=7.9, 3.2 Hz, ArH), 7.86 (d, 2H, $J$=3.2 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 22.2 (2×$CH_3$), 28.6, 45.8, 118.8 (2×CH), 125.9, 129.0 (2×CH), 137.1, 163.1, 165.0; IR (KBr) 3193 (m), 2935 (m), 1717 (s, C=O), 1575 (s, C=N), 1489 (m), 1283 (m), 979 (m), 802 (m), 763 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 359 (M+2, 4), 358 ($M^+$, 8), 357 (M−2, 4), 344 (9),

315 (4), 278 (6), 254 (8), 253 (14), 252 (8), 201 (9), 184 (5), 174 (28), 173 (32), 171 (4), 145 (3), 130 (6), 119 (4), 105 (19), 91 (32), 78 (10), 77 (100), 67 (11), 64 (10), 51 (24). Anal. Calcd for $C_{12}H_{12}Br_2N_2O$: C, 40.03; H, 3.36; N, 7.78. Found: C, 40.06; H, 3.32; N, 7.81.

*3.3.4. 4,4-Dibromo-1,3-diphenyl-2-pyrazolin-5-one (**5d**)*[10]. Mp (purified by column chromatography on silica gel) 128–130 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.27 (d, 1H, $J$=7.6 Hz, ArH), 7.42–7.54 (m, 5H, ArH), 7.99 (d, 2H, $J$=7.8 Hz, ArH), 8.23 (d, 2H, $J$=7.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 42.7, 119.1 (2×CH), 126.4, 127.2 (2×CH), 128.9 (2×CH), 129.2 (2×CH), 131.7, 137.0, 137.1, 153.5, 165.7; IR (KBr) 3391 (s), 3184 (m), 1632 (s, C=O), 1575 (s, C=N), 1404 (m), 1112 (m), 773 (m), 704 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 397 (M+2, 18), 395 (M$^+$, 36), 393 (M−2, 18), 338 (14), 315 (45), 263 (9), 219 (66), 241 (15), 165 (19), 154 (39), 119 (52), 95 (93), 69 (99), 55 (100); HRMS calcd for $C_{15}H_{10}Br_2N_2O$ 391.9160, found 391.9157.

*3.3.5. 4,4-Dibromo-1-(2′-methylphenyl)-3-phenyl-2-pyrazolin-5-one (**5e**).* Mp (purified by column chromatography on silica gel) 104–106 °C; $^1$H NMR ($CD_3OD$, 200 MHz) $\delta$ 2.23 (s, 3H, $CH_3$), 7.47–7.52 (m, 7H, ArH), 7.96–8.01 (m, 2H, ArH); $^{13}$C NMR ($CD_3OD$, 50 MHz) $\delta$ 16.0, 126.1 (2×CH), 127.0, 127.6, 128.0, 128.5, 129.0 (2×CH), 130.6, 131.0, 131.1, 132.5, 136.6, 149.8, 157.5; IR (KBr) 3198 (s), 2959 (m), 1717 (s, C=O), 1542 (s, C=N), 1319 (m), 1194 (m), 980 (m), 761 (m) cm$^{-1}$; MS $m/z$ (relative intensity) 410 (M+2, 6), 408 (M$^+$, 12), 406 (M−2, 6), 365 (2), 327 (74), 311 (3), 283 (7), 249 (53), 219 (10), 191 (6), 171 (6), 145 (12), 129 (36), 105 (24), 91 (100), 65 (26), 51 (16). Anal. Calcd for $C_{16}H_{12}Br_2N_2O$: C, 47.09; H, 2.96; N, 6.86. Found: C, 47.13; H, 2.92; N, 6.90.

*3.3.6. 4,4-Dibromo-1-(4′-methoxyphenyl)-3-phenyl-2-pyrazolin-5-one (**5f**).* Mp (purified by column chromatography on silica gel) 108–110 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.81 (s, 3H, $CH_3$), 6.97 (d, 2H, $J$=7.2 Hz, ArH), 7.48–7.51 (m, 3H, ArH), 7.85 (d, 2H, $J$=7.2 Hz, ArH), 8.19 (d, 2H, $J$=7.8 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 42.6, 55.6, 114.2 (2×CH), 121.0 (2×CH), 127.1 (2×CH), 127.3, 128.8 (2×CH), 130.2, 131.5, 153.4, 157.9, 165.4; IR (KBr) 3194 (s), 2959 (m), 1717 (s, C=O), 1508 (s, C=N), 1251 (m), 1006 (m) cm$^{-1}$; MS $m/z$ (relative intensity) 427 (M+2, 2), 425 (M$^+$, 4), 423 (M−2, 2), 345 (99), 343 (97), 266 (82), 265 (53), 235 (14), 221 (17), 209 (6), 162 (8), 160 (15), 158 (8), 135 (48), 129 (39), 121 (30), 107 (100), 102 (17), 92 (38), 77 (66), 64 (19). Anal. Calcd for $C_{16}H_{12}Br_2N_2O_2$: C, 45.31; H, 2.85; N, 6.61. Found: C, 45.27; H, 2.89; N, 6.57.

*3.3.7. 4,4-Dibromo-1-(2′,4′-dinitrophenyl)-3-phenyl-2-pyrazolin-5-one (**5g**).* Mp (purified by column chromatography on silica gel) 182–184 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.22–7.28 (m, 1H, ArH), 7.45–7.52 (m, 2H, ArH), 7.86 (dd, 1H, $J$=7.8, 3.7 Hz, ArH), 7.97 (d, 1H, $J$=7.8 Hz, ArH), 8.22–8.27 (m, 2H, ArH), 8.61 (d, 1H, $J$=3.7 Hz, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 38.4, 121.2, 124.9, 126.3 (2×CH), 127.5, 129.2 (2×CH), 129.8, 131.7, 134.3, 141.9, 144.6, 157.2, 169.9; IR (KBr) 3195 (m), 2926 (s), 1749 (s, C=O), 1510 (s, C=N), 1339 (m), 1169 (m), 1079 (m), 892 (m), 685 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 486 (M+2, 9), 484 (M$^+$, 18), 482 (M−2, 9), 405 (98), 325 (89), 279 (11), 205 (17), 147 (19), 129 (100), 103 (88), 93 (29), 77 (80), 63 (22), 51 (31); HRMS calcd for $C_{15}H_8Br_2N_4O_5$ 481.8861, found 481.8857.

*3.3.8. 4,4-Dibromo-1-(2′,4′,6′-trichlorophenyl)-3-phenyl-2-pyrazolin-5-one (**5h**).* Mp (purified by column chromatography on silica gel) 90–91 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.46–7.52 (m, 5H, ArH), 8.11–8.16 (m, 2H, ArH); IR (KBr) 3198 (m), 1749 (s, C=O), 1557 (s, C=N), 1470 (m), 1183 (m), 1064 (m), 815 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 502 (M+2, 4), 500 (M$^+$, 8), 498 (M−2, 4), 419 (67), 416 (100), 391 (14), 389 (21), 387 (11), 339 (46), 303 (20), 273 (21), 221 (4), 207 (27), 179 (57), 158 (29), 129 (63), 103 (68), 75 (33), 51 (25). Anal. Calcd for $C_{15}H_7Br_2Cl_3N_2O$: C, 36.22; H, 1.42; N, 5.63. Found: C, 36.45; H, 1.56; N, 5.31.

*3.3.9. 4,4-Dibromo-3-phenyl-2-pyrazolin-5-one (**5i**).* Mp 147–149 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 7.49–7.54 (m, 3H, ArH), 8.11–8.16 (m, 2H, ArH); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 40.5, 126.3 (2×CH), 127.9, 128.3 (2×CH), 130.7, 154.3, 170.5; IR (KBr) 3156 (m), 1742 (s, C=O), 1541 (m, C=N), 1271 (m), 865 (m), 742 (m), 692 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 320 (M+2, 8), 318 (M$^+$, 16), 316 (M−2, 8), 240 (61), 209 (7), 182 (13), 160 (41), 129 (100), 102 (86), 77 (44), 75 (46), 63 (12), 51 (39). Anal. Calcd for $C_9H_6Br_2N_2O$: C, 34.00; H, 1.90; N, 8.81. Found: C, 33.97; H, 1.94; N, 8.78.

*3.3.10. 4,4-Dibromo-3-phenyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (**5j**).* Mp (purified by column chromatography on silica gel) 180–182 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.16–7.27 (m, 1H, ArH), 7.43–7.50 (m, 3H, ArH), 7.79–7.87 (m, 1H, ArH), 7.90–7.99 (m, 1H, ArH), 8.21–8.26 (m, 2H, ArH), 8.55–8.58 (m, 1H, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 42.4, 114.9, 122.0, 127.0, 127.5 (2×CH), 127.8, 128.7 (2×CH), 131.8, 138.5, 148.9, 154.2, 165.9; IR (KBr) 3200 (s), 2929 (m), 1718 (s, C=O), 1558 (s, C=N), 1409 (m), 1311 (m), 1268 (m), 974 (m), 864 (m), 828 (m), 812 (m), 739 (m), 690 (m) cm$^{-1}$; EIMS $m/z$ (relative intensity) 395 (M$^+$, 2), 320 (8), 318 (16), 316 (8), 237 (46), 209 (7), 182 (12), 160 (12), 129 (100), 102 (69), 75 (32), 51 (21); HRMS calcd for $C_{14}H_9Br_2N_3O$ 392.9112, found 392.9109.

*3.3.11. 4,4-Dibromo-3-phenyl-1-(3-isoquinolinyl)-2-pyrazolin-5-one (**5k**).* Mp (purified by column chromatography on silica gel) 131–133 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.38–7.58 (m, 5H, ArH) 7.70–7.85 (m, 3H, ArH) 8.09–8.16 (m, 1H, ArH) 8.27–8.34 (m, 2H, ArH); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 42.5, 113.7, 126.7, 126.9, 127.1, 127.5, 127.6 (2×CH), 128.7 (2×CH), 129.1, 130.4, 131.9, 138.9, 146.8, 148.0, 154.3, 166.2; IR (KBr) 3045 (m), 2884 (m), 1751 (s, C=O), 1645 (m, C=N), 1503 (m), 1429 (m), 1383 (m), 1290 (m), 899 (m), 823 (m), 686 (m) cm$^{-1}$. Anal. Calcd for $C_{18}H_{11}Br_2N_3O$: C, 48.57; H, 2.49; N, 9.44. Found: C, 48.24; H, 2.64; N, 9.31.

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