Dibromination of 5-Pyrazolones and 5-Hydroxypyrazoles *via* Dibromoisocyanuric Acid

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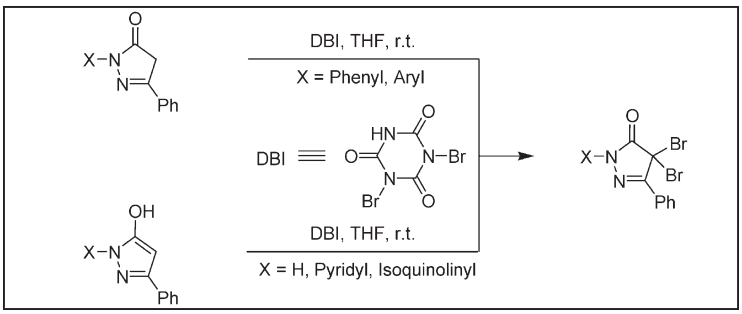

A safe and efficient method was developed for the dibromination of pyrazolones and 5-hydroxypyrazoles by use of dibromoisocyanuric acid (DBI). The reaction gave the corresponding dibrominated pyrazolones in excellent yields (≥91%).

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INTRODUCTION

Halogenated pyrazolone compounds attracted attentions for some of them displaying interesting biological activities [1]. Among the compounds, 4,4-dibromo-5-pyrazolone have been reported as fungicides against *Helminthosporium oryzae* [2], α-glucosidase inhibitors, and used for the treatment of tumor metastasis, AIDS, diabetes, hyperlipidemia, autoimmune disease, allergy, and rejection in organ transplant [3]. They are also useful synthetic intermediates for the preparation of diazo-dyes [4], and fused- [5] and spiro-hetercyclic compounds [6].

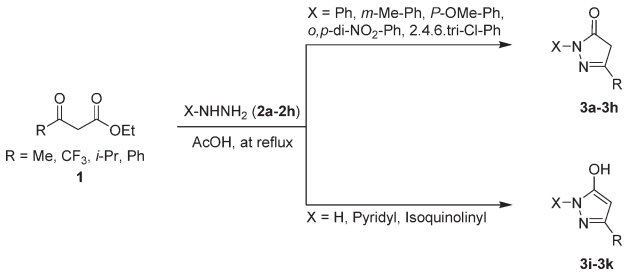
Traditional method for the synthesis of brominated pyrazolone is the use of Br_2 in acetic acid [7]. However, harsher conditions and manipulations with care are required. Use of the mild brominating reagent *N*-bromosuccinimide (NBS) [8b] or 1,3-dibromo-5,5-dimethylhydantoin [8c] does not also provide the corresponding dibrominated products in satisfactory yields as the monobrominated and coupling by-products were accompanied to form. As a mild brominating agent, dibromoisocyanuric acid (DBI) has been reported to brominates primary amides [9] and *N*,*N*-dimethylanilines [10]. For the structural similarity of the substrates, it is possible to extend the reagent to pyrazolones. Herein, we report an efficient method for the dibromination of pyrazolones and 5-hydroxypyrazoles by using DBI. A series of 4,4-dibromo-5-pyrazolones could be obtained in excellent yields (≥91%) by this method. Comparison with the use of NBS as the brominating agent, we found the use of DBI toward pyrazolones was more efficient.

RESULTS AND DISCUSSION

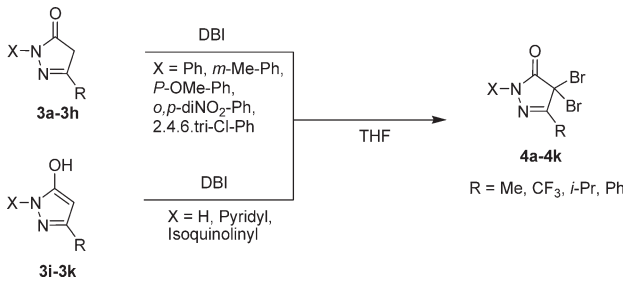
5-Pyrazolones were prepared as the substrates for the investigation of dibromination by DBI through tandem condensation and thermal cyclization following the reported procedure [11]. α-Keto esters **1** were heated at reflux in AcOH with equal equivalent of arylhydrazines **2a**–**2h** possessing various substituents including *m*-Me, *p*-OMe, *o*, *p*-di-NO_2, and 2,4,6,-trichloro at the phenyl ring for 4.0 h. The corresponding 5-pyrazolones (keto form) were obtained in good to excellent yields (>75%, see Scheme 1 and Chart 1) [11]. Use of hydrazine, and pyridyl and isoquinolinyl hydrazines as the starting material provided the corresponding 5-hydroxypyrazoles **3i**–**3k** (enol form) in >86% yields (see Scheme 1, and Chart 1). The experiment results were consistent with the literature reported [12].

To search an efficient and reproducible procedure, we carried out a model study by treating 5-pyrazolone (**3a**)

Scheme 1



Scheme 2



with DBI [13] in THF at room temperature for 30 min (see Chart 1 and Scheme 2). The reaction afforded the desired 4,4-dibromo-5-pyrazolone (**4a)** in 95% yield. Compound **4a** was fully characterized by spectroscopic method and the results were consistent with the reported data from literature [14]. In a control experiment by reacting **3a** with NBS, the reaction was less efficient which provided **4a** in 78% yield.

By using the newly developed method shown in Scheme 2, we successful applied this synthetic strategy to 5-pyrazolones **3b–3h** with *N*-substituted group, including *m*-Me, *p*-OMe, *o*,*p*-di-NO_2, and 2,4,6-trichloro. The corresponding products **4b–4h** were obtained in the ≥91% yields (see Table 1). This synthetic strategy is applicable to 5-hydroxypyrazole (enol form of 5-pyrazolone) that bear *N*-substituted group, such as H, pyridyl, and isoquinolinyl (**3i–3k**). The desired compounds **4i–4k** were afforded in 91–95% yields and fully characterized by spectroscopic methods. For example, compound **4k** possessed characterization absorptions at δ 42.5 ppm for O=C—$^{13}C(Br)_2$ in pyrazolone ring and IR absorptions showed peaks at 1751 cm^{-1} for stretching of the —C=O group.

We proposed a plausible mechanism for the dibromination of 5-pyrazolones by use of DBI as shown in Scheme 3. When 5-hydroxypyrazoles **3a–3h** were treated with DBI, the compounds favored the enol form in the acidic condition and underwent the smoothly nucleophilic substitution reaction to generate the corresponding mono-bromo-5-pyrazolone intermediates **6** with *N*-monobromoisocyanuric acid **5**. Application of 5-hydroxy-3-phenyl-1*H*-pyrazole (**3i**), 5-hydroxy-3-phenyl-1-(pyrid-2-yl)-1*H*-pyrazole (**3j**), and 5-hydroxy-3-phenyl-1-(3-isoquinolinyl)-1*H*-pyrazole (**3k**) as the model demonstrated that the enol species could also proceeded the nucleophilic substitution in the same reaction condition. For the further conjunction conversion, mono-bromo-5-pyrazolones **6** were converted to the mono-bromo-5-hydroxypyrazoles **7** under the reaction mixture. Finally, mono-bromo-5-hydroxypyrazole intermediates **7** consequential trapped the secondary equivalent bromine from the *N*-monobromoisocyanuric acid **5** to generate final dibrominated products **4a–4k** and cyanuric acid **8**. Cyanuiric acid **8** can be isolated by column chromatography and identified by IR and ^{13}C NMR spectroscopic methods to demonstrate the plausible mechanism.

In conclusion, we have successfully developed a dibrominating method for the conversion of the keto form pyrazolone and the enol form 5-hydroxypyrazole substrates by use of DBI as the reagent. The reaction provided 4,4-dibromo-pyrazolones **4a–4k** in excellent yields (≥91%). This newly developed bromination method was a safe and efficient would be useful in the large-scale preparation of the dibrominated pyrazolones.

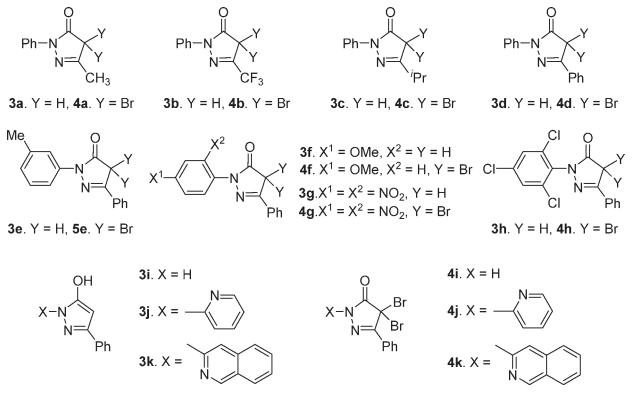


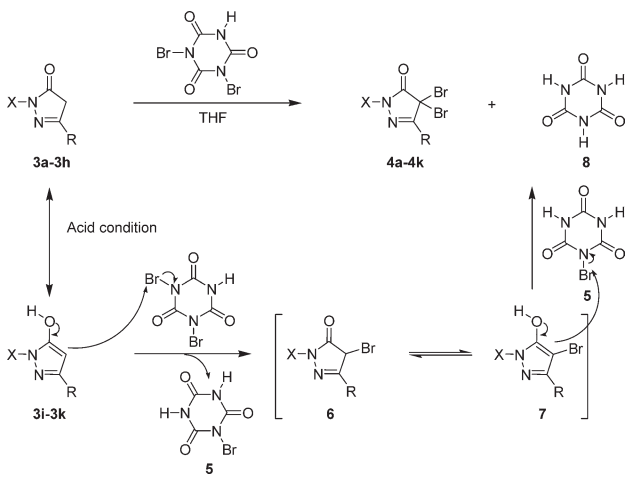
Chart 1

Table 1

The results of bromination by using dibromoisocyanuric acid (DBI).

5-Pyrazolones (**3a–3h**) or 5-hydroxypyrazoles (**3i–3k**)			Dibromination (**4a–4k**)	
Compounds	X	R	Products	Yields (%)
3a	Ph	Me	**4a**	95
3b	Ph	CF_3	**4b**	94
3c	Ph	*i*-Pr	**4c**	98
3d	Ph	Ph	**4d**	96
3e	*m*-Me-Ph	Ph	**4e**	94
3f	*p*-OMe-Ph	Ph	**4f**	93
3g	*o*,*p*-*di*-NO_2-Ph	Ph	**4g**	97
3h	2,4,6,-*tri*-Chloro-Ph	Ph	**4h**	92
3i	H	Ph	**4i**	93
3j	Pyridyl	Ph	**4j**	95
3k	Isoquinolinyl	Ph	**4k**	91

Scheme 3



EXPERIMENTAL

General procedure. All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from Mallinckrodt Chemical Co. Dry tetrahydrofuran (reagent grade) was used. The following compounds were purchased from Acoros Chemical Co: *o*-tolyhydrazine hydrochoide, *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 acietoacetate 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 FTIR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm−1 absortion. 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 *d6*-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by used of $CDCl_3$, CH_3OD, and *d6*-DMSO as solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl3 triplet (δ 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.

Standard procedure for dibromination to prepare 4,4-dibromo-5-pyrazolone derivatives 4a–4k. To a solution of pyrazolones **3a–3h** or 5-hydroxypyrazoles **3i–3k** (1.0 equiv) in THF (20 mL) was added DBI (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 redissolved 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 **4a–4k** as solids in 91–98% yields.

4,4-Dibromo-3-methyl-1-phenyl-2-pyrazolin-5-one (4a). To a solution of pyrazolones **3a** (20 g, 0.114 mol, 1.0 equiv) in THF (150 mL) was added DBI (69.2 g, 0.242 mol, 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 redissolved in CH_2Cl_2 (200 mL). The solution was washed with H_2O (80 mL × 2), brine (80 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 **4a** as solids in 95 % yields. mp 80–82°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s, 3 H, CH_3), 7.21 (d, 1 H, J = 2.6 Hz, ArH), 7.39 (dd, 2 H, J = 7.4, 2.6 Hz, ArH), 7.84 (d, 2 H, J = 7.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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.

4,4-Dibromo-1-phenyl-3-trifluoro-2-pyrazolin-5-one (4b). mp 119–121°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24–7.52 (m, 3 H, ArH), 7.81 (d, 2 H, 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: 31.46; H: 1.65; N: 6.94.

4,4-Dibromo-3-isopropyl-1-phenyl-2-pyrazolin-5-one (4c). mp 77–79°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44 (d, 6 H, J = 7.2 Hz, 2 × CH_3), 3.06 (m, 1 H, $CHMe_2$), 7.23 (d, 1 H, J = 7.9 Hz, ArH), 7.41 (dd, 2 H, J = 7.9, 3.2 Hz, ArH), 7.86 (d, 2 H, J = 3.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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.

4,4-Dibromo-1,3-diphenyl-2-pyrazolin-5-one (4d). mp 128–130°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (d, 1 H, J = 7.6 Hz, ArH), 7.42–7.54 (m, 5 H, ArH), 7.99 (d, 2 H, J = 7.8 Hz, ArH), 8.23 (d, 2 H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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^+, 30), 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. Anal. Calcd for $C_{15}H_{10}Br_2N_2O$; C: 45.72; H: 2.56; N: 7.11, Found: C: 45.76; H: 2.59; N: 7.15.

4,4-Dibromo-1-(2-methyl)-phenyl-3-phenyl-2-pyrazolin-5-one (4e). mp 104–106°C; ^{1}H NMR (CD_3OD, 200 MHz) δ 2.23 (s, 3 H, CH_3), 7.47–7.52 (m, 7 H, ArH), 7.96–8.01 (m, 2 H, ArH); ^{13}C NMR (CD_3OD, 50 MHz) δ 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.

4,4-Dibromo-1-(4-methoxy)-phenyl-3-phenyl-2-pyrazolin-5-one (4f). mp 108–110°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3 H, CH_3), 6.97 (d, 2 H, J = 7.2 Hz, ArH), 7.48–7.51 (m, 3 H, ArH), 7.85 (d, 2 H, J = 7.2 Hz, ArH), 8.19 (d, 2 H, J = 7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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.

4,4-Dibromo-1-(2,4-dinitro)-phenyl-3-phenyl-2-pyrazolin-5-one (4g). mp 182–184°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.22–7.28 (m, 1 H, ArH), 7.45–7.52 (m, 2 H, ArH), 7.86 (dd, 1 H, J = 7.8, 3.7 Hz, ArH), 7.97 (d, 1 H, J = 7.8 Hz, ArH), 8.22–8.27 (m, 2 H, ArH), 8.61 (d, 1 H, J = 3.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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^+, 17), 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. Anal. Calcd for $C_{15}H_8Br_2N_4O_5$; C: 37.22; H: 1.67; N: 11.57, Found: C: 37.26; H: 1.71; N: 11.61.

4,4-Dibromo-1-(2,4,6-trichloro)-phenyl-3-phenyl-2-pyrazolin-5-one (4h). mp 90–91°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46–7.52 (m, 5 H, ArH), 8.11–8.16 (m, 2 H, 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.

4,4-Dibromo-3-phenyl-2-pyrazolin-5-one (4i). mp 147–149°C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.49–7.54 (m, 3 H, ArH), 8.11–8.16 (m, 2 H, ArH); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 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.

4,4-Dibromo-3-phenyl-1-(pyrid-2-yl)-2-pyrazolin-5-one (4j). mp 180–182°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.16–7.27 (m, 1 H, ArH), 7.43–7.50 (m, 3 H, ArH), 7.79–7.87 (m, 1 H, ArH), 7.90–7.99 (m, 1 H, ArH), 8.21–8.26 (m, 2 H, ArH), 8.55–8.58 (m, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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.

4,4-Dibromo-3-phenyl-1-(3-isoquinolinyl)-2-pyrazolin-5-one (4k). mp 131–133°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–7.58 (m, 5 H, ArH) 7.70–7.85 (m, 3 H, ArH) 8.09–8.16 (m, 1 H, ArH) 8.27–8.34 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 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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REFERENCES AND NOTES

[1] Kakiuchi, Y.; Sasaki, N.; Satoh-Masuoka, M.; Murofushi, H.; Murakami-Murofushi, K. Biochem Biophys Res Commun 2004, 320, 1351.

[2] Sarojbasinidas, A. N.; Mishra, C. R.; Mittra, A. S. J Indian Chem Soc 1977, LIV, 485.

[3] Fuminori, K.; Hirohiko, K. Jpn. Pat.45588, 1998.

[4] Kirscuke, K.; Luize, G.; Schmttz, E. J Park Chem 1984, 326, 367.

[5] Chande, M. S.; Bhandari, J. D.; Joshi, V. R. Indian J Chem B 1993, 32B, 1218.

[6] El-Saraf, G. A.; El-Sayed, A. M. Heteroat Chem 2003, 14, 211.

[7] (a) Karci, F.; Ertan, N. Dyes Pigments 2002, 55, 99; (b) Ho, Y. W. Dyes Pigments 2004, 64, 223.

[8] (a) Ahmed, S. A.; Award, D. M. A.; Abdel-Wahab, Aboel-Mahab, A. Chem Commun 2002, 1, 84; (b) Edward, M. K.; Dov, F.; Marcia, B. S.; Israel, G. J Org Chem 1982, 47, 214; (c) Spitulnik, M. J. Synthesis 1985, 47, 299.

[9] Demko, Z. P.; Bartsch, M.; Sharpless, K. B. Org Lett 2000, 15, 2221.

[10] Rossevear, J.; Wishire, J. F. K. Aust J Chem 1972, 30, 1561.

[11] (a) Wang, X.-j.; Tan, J.; Grozinger, K. Tetrahedron Lett 2000, 41, 4713; (b) DeRuiter, J.; Carter, D. A.; Arledge, W. S.; Sullivan, P. J. J Heterocycl Chem 1987, 24, 149; (c) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; López, B.; Acero, N.; Llinares, F.; Mingarro, D. M. Bioorg Med Chem 2006, 14, 9.

[12] (a) McFerrin, C. A.; Hammer, R. P.; Fronczek, F. R.; Watkins, S. F. Acta Cryst 2006, E62, 2518; (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. J Med Chem 2007, 50, 5053; (c) Mojtahedi, M. M.; Javadpour, M. Abaee, M. S. Utrason SonoChem 2008, 15, 828; (d) Basaif, S. A.; Hassan, M. A.; Gobouri, A. A. Dyes Pigments 2007, 72, 387.

[13] Gottardi, W. Monatsh Chem 1975, 106, 611.

[14] Kirscuke, K.; Luize, G.; Schmttz, E. J Park Chem 1984, 326, 367.