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# A novel one-pot approach to oxidative aromatization and bromination of pyrazolidin-3-one with HBr-$H_2O_2$ system

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**Abstract:** An efficient and green one-pot method for the oxidative aromatization and bromination of pyrazolidin-3-ones under mild conditions with a HBr-$H_2O_2$ system was developed. A mechanism was proposed.

**Keywords:** aromatization; bromination; bromopyrazol; hydrogen bromide; hydrogen peroxide; one-pot; oxidative; pyrazolidin-3-one.

## Introduction

Pyrazole derivatives attract attention due to their excellent pharmacological properties [1–4]. Halogenated pyrazolols [5, 6], especially 4-bromo derivatives, are precursors for the synthesis of functionalized pyrazoles [7–9], such as pharmaceuticals [10], multifunctional materials [11, 12], fused- [13] and spiro-heterocyclic compounds [14]. Various protocols for the synthesis of brominated pyrazolols have been reported. However, bromination of pyrazolols with $Br_2$ in acetic acid is carried out under harsh conditions and requires careful manipulation [15]. Efforts have been made by Ahmed et al. [16] to use the photolysis of *N*-bromosuccinimide as the source of bromine [16]. Due to the formation of the coupling by-products, bromopyrazolols are afforded in low yields. Although *N*-bromobenzamide [17] and dibromoisocyanuric acid [18] have also been explored as mild brominating agents for pyrazolols, these approaches have met with limited success.

Recently, pyrazolidinones have been reported as substrates for the synthesis of pyrazolols [7, 11, 12, 19–23]. Unfortunately, few efficient methods for direct access to 4-bromopyrazolol from pyrazolidinone have been reported. Traditionally, there are two steps in the synthesis of 4-bromopyrazolol from pyrazolidinone [7, 11, 12] that involve aromatization of pyrazolidin-3-ones to give pyrazol-3-ols and bromination of pyrazol-3-ols [7]. This protocol requires the use of a transition-metal catalyst, extremely toxic liquid bromine, a long reaction time, multi-step manipulations and the final yield is only moderate. In recent years, brominations with safe bromination reagents and green co-oxidants have received growing attention because of their greenness and high efficiency [24]. Herein, we report a novel one-pot, metal-free, atom-economic and highly effective method for the preparation of 4-bromopyrazol-3-ol from pyrazolidin-3-one using a HBr-$H_2O_2$ system under mild conditions.

## Results and discussion

The starting compounds **1** (Scheme 1) were commercially available or easily prepared according to previously published procedures [7, 11, 12, 19–23]. Initially, 1-(4-chlorophenyl)-pyrazolidin-3-one (**1a**) was treated with various amounts of hydrogen peroxide and hydrobromic acid using various solvents. It was found that the use of different solvents including carbon tetrachloride, chloroform, dichloromethane, methanol and *N,N*-dimethylformamide had little effect on the outcome, affording the yield of the product **2a** in the range from 72% to 90%. Nevertheless, the highest yield of 90% was obtained for the reaction conducted in chloroform. Under optimized conditions, the synthesis of **2a** was conducted in chloroform at 60°C using 3 equivalents of $H_2O_2$ and 1 equivalent of HBr.

Decreasing the amount of hydrogen peroxide to 1 equivalent or 2 equivalents resulted in a decrease of the yield of the product **2a**. On the other hand, an increase in the amount of hydrogen peroxide from 3 equivalents to 4 equivalents did not affect the yield. With the optimized reaction conditions for **2a**, a wide range of 4-bromo-3-hydroxypyrazolidines were synthesized (Scheme 1). The reaction proceeds well with pyrazolidin-3-ones containing a phenyl group, a substituted phenyl group or a pyridinyl

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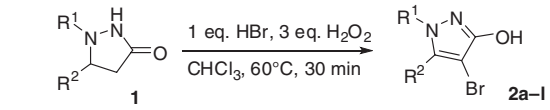


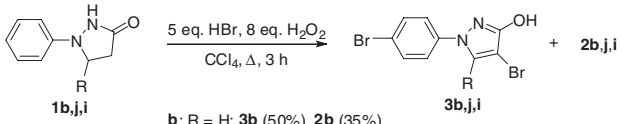

**2a**: $R^1$ = 4-Cl-$C_6H_4$, $R^2$ = H
**2b**: $R^1$ = Ph, $R^2$ = H
**2c**: $R^1$ = 4-F-$C_6H_4$, $R^2$ = H
**2d**: $R^1$ = 4-Me-$C_6H_4$, $R^2$ = H
**2e**: $R^1$ = 3-Cl-pyridin-2-yl, $R^2$ = H
**2f**: $R^1$ = 4-Cl-$C_6H_4$, $R^2$ = Me
**2g**: $R^1$=4-Cl-$C_6H_4$, $R^2$ = Ph
**2h**: $R^1$ = 4-Cl-$C_6H_4$, $R^2$ = MeO
**2i**: $R^1$ = Ph, $R^2$ = Ph
**2j**: $R^1$ = Ph, $R^2$ = Me
**2k**: $R^1$= 4-Me-$C_6H_4$, $R^2$ = Me
**2l**: $R^1$ = H, $R^2$ = Me

**Scheme 1**

group. With an increase in the electron-donating capability of the substituent at the 5-position of pyrazolidin-3-ones (MeO > $CH_3$ > H), the efficiency of the reaction is increased in the same order.

Interestingly, when the reaction with 5 equivalents of HBr was carried out for 3 h (Scheme 2), the corresponding dibrominated products **3b,j** were obtained accompanied by the corresponding monobrominated products **2b,j** in moderate yields. However, in the case of compound **1i** only monobrominated product **2i** was acquired in high yield. For further confirmation of the structure of the series, a single crystal of **3j** was obtained and subjected to X-ray diffraction analysis (Figure 1).

To gain access to the mechanism, the experiments were carried out as shown in Scheme 3. When the




**b**: R = H; **3b** (50%), **2b** (35%)
**j**: R = Me; **3j** (58%), **2j** (33%)
**i**: R = Ph; **3i** (0%), **2i** (89%)

**Scheme 2**

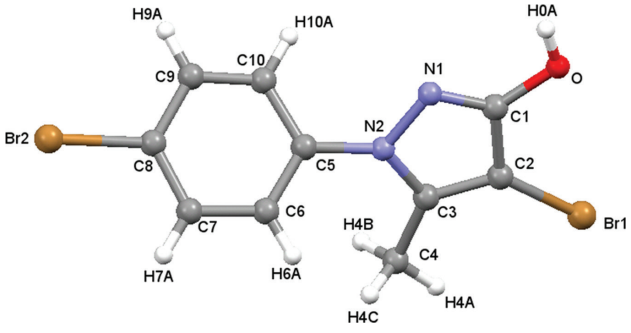
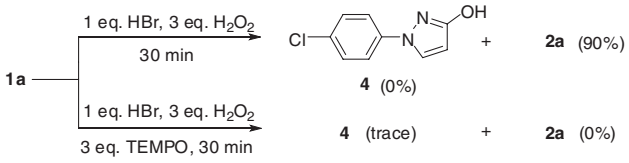
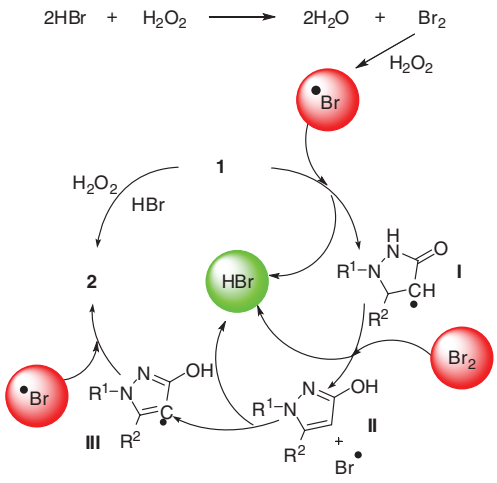



**Figure 1** Molecular structure of **3j** with atom labeling.




**Scheme 3**




**Scheme 4**

reaction under optimized conditions was performed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger, only a trace amount of 1-(4-chlorophenyl)-1*H*-pyrazol-3-ol (**4**) was detected, suggesting a radical pathway. This finding and previous reports [25–27], are consistent with the mechanism suggested in Scheme 4. First, compound **1** undergoes a reaction with a bromine radical to generate the corresponding radical intermediate **I**, which is subsequently converted to the substituted pyrazol-3-ol **II** by oxidation with molecular bromine. Then, in the presence of the bromine radical, the corresponding radical species **III** is generated from the intermediate compound **II**. Finally, the reaction of the intermediate product **III** with the bromide radical furnishes the observed 4-bromopyrazol-3-ol **2**.

## Conclusions

A green and efficient protocol to prepare substituted 4-bromo-pyrazol-3-ols **2** from pyrazolidin-3-ones **1** under mild conditions in excellent yields was described. The corresponding dibromination products **3b,j** were also obtained in moderate yields under harsh conditions.

# Experimental

Proton nuclear magnetic resonance ($^1$H NMR) spectra were obtained on a Bruker spectrometer operating at 600 MHz with dimethyl sulfoxide-$d_6$ as solvent and tetramethylsilane as internal standard. Infrared (IR) spectra were obtained using KBr disks on a Bomem Michelson Series Fourier-transform infrared spectrometer. The mass spectrometry (MS) data were recorded with an Agilent 7890A-5975C instrument. Melting points were obtained on an X-4 microscope electrothermal apparatus (Taike, China) and are uncorrected. Elemental analyses were carried out on a Vario EL III analyzer. Spectral data for compounds **2b**, **3b** and **4** are virtually identical with the reported values [9, 20, 28].

## Synthesis of 4-bromopyrazol-3-ones 2a–l

A mixture of **1a–l** (0.01 mol) in $CHCl_3$ (10 mL) and 40% hydrobromic acid (40%, 0.01 mol) was stirred at 60°C and treated dropwise for 10 min with an aqueous solution of $H_2O_2$ (30%, 0.03 mol), and stirring was continued for an additional 20 min. The resultant precipitate of **2a–l** was filtered off and crystallized from ethanol. The filtrate was concentrated and the residue was subjected to silica gel chromatography eluting with ethyl acetate/petroleum ether (10:1) to give an additional amount of **2a–l**.

**4-Bromo-1-(4-chlorophenyl)-1*H*-pyrazole-3-ol (2a)** White solid; mp 192–194°C; yield 90%; $^1$H NMR: δ 11.13 (s, 1H, OH), 8.58 (s, 1H, CH), 7.71 (d, $J$ = 9 Hz, 2H, Ar), 7.51 (d, $J$ = 9 Hz, 2H, Ar); IR: 3440, 2971, 1617, 1563, 1494, 1392, 1306, 1105 cm$^{-1}$; MS: $m/z$ 274.3 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_9H_6BrClN_2O$: C, 39.52; H, 2.21; N, 10.24. Found: C, 39.81; H, 2.03; N, 10.02.

**4-Bromo-1-phenyl-1*H*-pyrazole-3-ol (2b)** Yellow solid; mp 188–190°C; yield 91%; $^1$H NMR: δ 11.02 (s, 1H, OH), 8.54 (s, 1H, CH), 7.69 (d, $J$ = 8 Hz, 2H, Ar), 7.45 (t, $J$ = 8 Hz, 2H, Ar), 7.23 (t, $J$ = 8 Hz, 1H, Ar); IR: 3449, 2927, 1620, 1550, 1493, 1309, 1102 cm$^{-1}$; MS: $m/z$ 240.1 [(M + 1)$^+$, 100%].

**4-Bromo-1-(4-fluorophenyl)-1*H*-pyrazole-3-ol (2c)** White solid; mp 219–221°C; yield 89%; $^1$H NMR: δ 11.01 (s, 1H, OH), 8.51 (s, 1H, CH), 7.70 (m, 2H, Ar), 7.30 (t, $J$ = 9 Hz, 2H, Ar); IR: 3451, 2971, 1622, 1568, 1519, 1404, 1311, 1240, 1087 cm$^{-1}$; MS: $m/z$ 258.1 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_9H_6BrFN_2O$: C, 42.05; H, 2.35; N, 10.90. Found: C, 42.22; H, 2.21; N, 10.68.

**4-Bromo-1-(4-methylphenyl)-1*H*-pyrazole-3-ol (2d)** Yellow solid; mp 183–185°C; yield 92%; $^1$H NMR: δ 10.93 (s, 1H, OH), 8.47 (s, 1H, CH), 7.56 (d, $J$ = 8 Hz, 2H, Ar), 7.24 (d, $J$ = 8 Hz, 2H, Ar), 2.31 (s, 3H, $CH_3$); IR: 3454, 2964, 1625, 1548, 1381, 1327, 1082 cm$^{-1}$; MS: $m/z$ 254.2 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.31; H, 3.73; N, 10.88.

**4-Bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-3-ol (2e)** Yellow solid; mp 233–235°C; yield 91%; $^1$H NMR: δ 11.48 (s, 1H, OH), 8.49 (s, 1H, CH), 7.98 (d, $J$ = 8 Hz, 1H, Ar), 7.60 (d, $J$ = 8 Hz, 1H, Ar), 7.37 (d, $J$ = 8 Hz, 1H, Ar); IR: 3451, 2965, 1626, 1582, 1444, 1389, 1305, 1261, 1068 cm$^{-1}$; MS: $m/z$ 273.1 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_8H_5BrClN_3O$: C, 35.00; H, 1.84; N, 15.31. Found: C, 34.83; H, 2.02; N, 15.50.

**4-Bromo-5-methyl-1-(4-chlorophenyl)-1*H*-pyrazol-3-ol (2f)** Yellow solid; mp 221–223°C; yield 92%; $^1$H NMR: δ 10.80 (s, 1H, OH), 7.55 (m, 2H, Ar), 7.51 (m, 2H, Ar), 2.28 (s, 3H, $CH_3$); IR: 3455, 2978, 1617, 1545, 1510, 1393, 1102 cm$^{-1}$; MS: $m/z$ 288.2 [(M + 1)$^+$, 81%]. Anal. Calcd for $C_{10}H_8BrClN_2O$: C, 41.77; H, 2.80; N, 9.74. Found: C, 41.61; H, 2.93; N, 9.89.

**4-Bromo-5-phenyl-1-(4-chlorophenyl)-1*H*-pyrazol-3-ol (2g)** White solid; mp 253–255°C; yield 94%; $^1$H NMR: δ 11.07 (s, 1H, OH), 7.43 (m, 3H, Ar), 7.39 (d, $J$ = 9 Hz, 2H, Ar), 7.30 (m, 2H, Ar), 7.21 (d, $J$ = 9 Hz, 2H, Ar); IR: 3462, 2973, 1552, 1496, 1331, 1075 cm$^{-1}$; MS: $m/z$ 350.3 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{15}H_{10}BrClN_2O$: C, 51.53; H, 2.88; N, 8.01. Found: C, 51.34; H, 3.06; N, 8.22.

**4-Bromo-5-methoxy-1-(4-chlorophenyl)-1*H*-pyrazol-3-ol (2h)** Yellow solid; mp 228–230°C; yield 95%; $^1$H NMR: δ 11.37 (s, 1H, OH), 7.65 (m, 2H, Ar), 7.38 (m, 2H, Ar), 3.74 (s, 3H, $OCH_3$); IR: 3452, 2961, 1632, 1560, 1503, 1402, 1314, 1207, 1054 cm$^{-1}$; MS: $m/z$ 300.4 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{10}H_8BrClN_2O_2$: C, 39.57; H, 2.66; N, 9.23. Found: C, 39.48; H, 2.79; N, 9.38.

**4-Bromo-1,5-diphenyl-1*H*-pyrazol-3-ol (2i)** Yellow solid; mp 242–244°C; yield 93%; $^1$H NMR: δ 10.98 (s, 1H, OH), 7.41 (m, 3H, Ar), 7.29 (m, 5H, Ar), 7.14 (d, $J$ = 8 Hz, 2H, Ar); IR: 3453, 2965, 1624, 1541, 1444, 1335, 1252, 1085 cm$^{-1}$; MS: $m/z$ 314.1 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.37; H, 3.38; N, 8.71.

**4-Bromo-5-methyl-1-phenyl-1*H*-pyrazol-3-ol (2j)** White solid; mp 218–220°C; yield 91%; $^1$H NMR: δ 10.71 (s, 1H, OH), 7.49 (m, 4H, Ar), 7.36 (t, $J$ = 7 Hz, 1H, Ar), 2.27 (s, 3H, $CH_3$); IR: 3450, 2969, 1623, 1549, 1496, 1409, 1328, 1270, 1103 cm$^{-1}$; MS: $m/z$ 254.1 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.63; H, 3.81; N, 10.86.

**4-Bromo-5-methyl-1-(4-methylphenyl)-1*H*-pyrazol-3-ol (2k)** White solid; mp 232–234°C; yield 92%; $^1$H NMR: δ 10.64 (s, 1H, OH), 7.35–7.28 (m, 4H, Ar), 2.35 (s, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$); IR: 3452, 2974, 1627, 1553, 1515, 1406, 1323, 1257, 1103 cm$^{-1}$; MS: $m/z$ 266.1 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.63; H, 4.36; N, 10.06.

**4-Bromo-5-methyl-1*H*-pyrazol-3-ol (2l)** White solid; mp 192–194°C; yield 85%; $^1$H NMR: δ 2.09 (s, 3H, CH); IR: 2060–3270, 1587, 1253, 1172, 1053 cm$^{-1}$; MS: $m/z$ 176.9659 [(M + 1)$^+$, 100%). Anal. Calcd for $C_4H_5BrN_2O$: C, 27.14; H, 2.85; N, 15.83. Found: C, 27.26; H, 2.96; N, 15.66.

## Synthesis of 4-bromo-1-(4-bromophenyl)pyrazol-3-ones 3b,j

A mixture of **1b,j** (0.01 mol), $CCl_4$ (10 mL) and hydrobromic acid (40%, 0.05 mol) was stirred, heated under reflux and treated dropwise with an aqueous solution of $H_2O_2$ (30%, 0.08 mol) for 3 h. After concentration under reduced pressure, the residue was chromatographed on silica gel eluting with ethyl acetate/petroleum ether (10:1) to give **3b,j**.

**4-Bromo-1-(4-bromophenyl)-1*H*-pyrazole-3-ol (3b)** Yellow solid; mp 199–201°C; yield 50%; $^1$H NMR: δ 11.17 (s, 1H, OH), 8.62 (s, 1H, CH), 7.69 (m, 4H, Ar); IR: 3458, 2962, 1624, 1556, 1494, 1390, 1302, 1209, 1048 cm$^{-1}$; MS: $m/z$ 318.9 [(M + 1)$^+$, 100%].

**4-Bromo-5-methyl-1-(4-bromophenyl)-1*H*-pyrazol-3-ol (3j)** White solid; mp 243–245°C; yield 58%; $^1$H NMR: δ 10.82 (s, 1H, OH), 7.68 (d, *J* = 9 Hz, 2H, Ar), 7.45 (d, *J* = 9 Hz, 2H, Ar), 2.28 (s, 3H, $CH_3$); IR: 3446, 2971, 1628, 1547, 1510, 1395, 1322, 1261, 1108 cm$^{-1}$; MS: *m/z* 330.3 [(M + 1)$^+$, 100%]. Anal. Calcd for $C_{10}H_8Br_2N_2O$: C, 36.18; H, 2.43; N, 8.44. Found: C, 36.33; H, 2.61; N, 8.28.

**1-(4-Chlorophenyl)-1*H*-pyrazol-3-ol (4)** White solid; mp 189–191°C; $^1$H NMR: δ 10.32 (s, 1H, OH), 8.24 (d, *J* = 3 Hz, 1H, CH), 7.70 (d, *J* = 9 Hz, 2H, Ar), 7.48 (d, *J* = 9 Hz, 2H, Ar), 5.84 (d, *J* = 3 Hz, 1H, CH); IR: 3438, 2976, 1630, 1545, 1489, 1382, 1245, 1057, 945, 757 cm$^{-1}$; MS: *m/z* 195.7 [(M + 1)$^+$, 100%].

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