# Synthesis of 2-Alkylpyrazole-1-oxides: A Facile Access to 1-Alkyl-5-halopyrazoles

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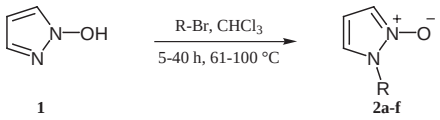
**Abstract:** Selective *N*-alkylation of 1-hydroxypyrazole **1** into the corresponding 2-alkyl-pyrazole-1-oxides **2a–f** has been achieved by treatment with alkyl bromides in the absence of base. Subsequent deoxygenation/halogenation into 1-alkyl-5-halopyrazoles **3a–d** and **4a–d** using phosphorus oxyhalides is described.

**Key words:** pyrazoles, alkylations, halogenation, deoxygenation, *N*-oxides

Traditionally 2-alkylpyrazol-1-oxides devoid of ring substituents have been prepared by peracid oxidation of the corresponding 1-alkylpyrazoles.[1,2] Chromatographic purification had to be involved and yields never exceeded 16% due to the fact that the first formed pyrazole-1-oxide reacted with additional peracid to give oxygen and the starting 1-alkylpyrazole.[1] We have previously reported that 1-hydroxypyrazole (**1**) undergoes selective *O*-alkylation upon treatment with an alkyl halide in the presence of a base. During these investigations we observed that **1** was selectively *N*-benzylated if the reaction with benzyl bromide was performed in the absence of a base at 80 °C.[3]

We now wish to report that **1** in the absence of a base undergoes selective *N*-alkylation with a variety of alkylating agents providing the corresponding 2-alkylpyrazole-1-oxides **2a–f** in 33% to 94% yield depending on the alkylating agent. Subsequent treatment with a phosphorus oxyhalide produced cleanly otherwise difficultly accessible 1-alkyl-5-halopyrazoles in 70% to 98% yield.[4] The *N*-alkylations of **1** were performed in chloroform at 60–100 °C in screw-cap sealed vessels[5] using an excess of the alkylating agent (Table 1). The more reactive alkyl bromides gave excellent yields (Table 1, entries 1–4) whereas butyl bromide and isopropyl bromide produced the corresponding *N*-oxides **2e** and **2f** in moderate yields (Table 1, entries 5 and 6), possibly because of decomposition due to the elevated reaction temperature. Attempts to use the more reactive alkyl iodides such as e.g. methyl iodide resulted in dark reaction mixtures and formation of byproducts. All the *N*-oxides were stable, colorless crystalline compounds (except **2e** which was an oil) and tend to be hygroscopic.

**Table 1** Synthesis of 2-Alkylpyrazole-1-oxides **2a–f**




**1** **2a-f**

| Entry | R | Conditions[a] T(°C) | t(h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4CH_2$ | 61 | 5 | **2a** | 94 |
| 2 | benzyl | 80[c] | 19 | **2b** | 82[3] |
| 3 | allyl | 80[c] | 18 | **2c** | 86 |
| 4 | Me | 80[c] | 12 | **2d** | 92 |
| 5 | Bu | 100[c] | 24 | **2e** | 49 |
| 6 | *i*-Pr | 100[c] | 40 | **2f** | 33 |

[a] All reactions were performed in $CHCl_3$ using excess RBr.
[b] Isolated yield.
[c] Performed in a screw-cap sealed vessel.

While 4-halogen substituted 1-alkylpyrazoles appear frequently in the literature[6] due to preferential electrophilic attack at C-4 of 1-alkylpyrazoles, the preparation of 5-halogen substituted 1-alkylpyrazoles devoid of substituents at C-3 and C-4 has only been reported in a few cases.[7–10] In particular, Ferguson et al. have reported a single example where a mixture of **3d** and presumably 3-chloro-1-methylpyrazole was obtained by treatment of **2d** with neat $POCl_3$ at 100 °C.[9]

The 2-alkylpyrazole-1-oxides **2a–f** represent an excellent source for the preparation of 5-chloro- or 5-bromo-substituted 1-alkylpyrazoles, since treatment of **2a–d** with phosphorus oxychloride or phosphorus oxybromide in chloroform at 0–50 °C produced 5-chloro or 5-bromo-substituted 1-alkylpyrazoles (Table 2). The reactions produced exclusively the 5-halo regioisomers. Yields were essentially quantitative although the products of lower molecular weight (Table 2, entries 5–8) could only be isolated in 70–85% yield due to their volatile nature.

The spectroscopic data of the 2-alkylpyrazole-1-oxides **2a–d** and 1-alkyl-5-halopyrazole-1-oxides **3a–d** and **4a–d** are given in Table 3. The 2-alkylpyrazole-1-oxides and the 1-alkyl-5-halopyrazoles described here appear only in scarce numbers in the literature which is surprising in view of the wide gamut of biological activities found for diazaheterocycles. The phosphorus oxyhalide mediated

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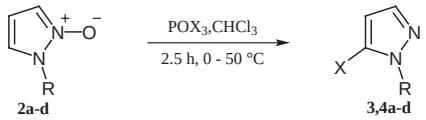
**Table 2** Synthesis of 1-Alkyl-5-halopyrazoles **3a–d** and **4a–d**[a]




| Entry | R | Reactant | X | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4CH_2$ | **2a** | Cl | **3a** | 93 |
| 2 | 4-$MeOC_6H_4CH_2$ | **2a** | Br | **4a** | 95 |
| 3 | Benzyl | **2b** | Cl | **3b** | 98 |
| 4 | Benzyl | **2b** | Br | **4b** | 87 |
| 5 | Allyl | **2c** | Cl | **3c** | 83 |
| 6 | Allyl | **2c** | Br | **4c** | 85 |
| 7 | Me | **2d** | Cl | **3d** | 70 |
| 8 | Me | **2d** | Br | **4d** | 78 |

[a] Reagents and conditions: All reactions were carried out in $CHCl_3$ under $N_2$ using 3–5 equiv $POX_3$ at 50 °C for 2 h 30 min.
[b] Isolated yield.

halogenation with simultaneous deoxygenation of 2-alkylpyrazole-1-oxides represents a straightforward procedure for obtaining otherwise difficultly accessible 1-alkyl-5-halopyrazoles, and provides a convenient route to new substitution patterns that may well afford products of interest for pharmaceutical applications.

$^1H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra were recorded on a Varian instrument using TMS as internal standard. Flash chromatography (FC) was performed using silica gel Merck 60 (230–400 mesh). Merck 60 type H was used for filtrations using silica gel. Melting points are uncorrected. All solvents and reagents were of analytical grade and purchased from Aldrich or Fluka and used without further purification except $CHCl_3$ wich was distilled prior to use. Petroleum ether refers to the fraction boiling at 80–100 °C. All products were colorless unless otherwise stated.

**2-(4-Methoxybenzyl)pyrazole-1-oxide (2a)**
4-Methoxybenzyl bromide[11] (43.6 g, 0.217 mol) and **1** (14.1 g, 0.168 mol) were dissolved in $CHCl_3$ (330 mL). The mixture was refluxed for 5 h under a static positive $N_2$ pressure of 0.4 bar. After cooling to r.t., the mixture was poured into toluene (400 mL) and extracted with 37% aq HCl (3 × 150 mL). The combined aqueous layers were washed with toluene (20 mL) and cautiously basified with 33% aq NaOH solution to pH >10 while cooling in an ice bath. The aqueous layer was extracted with $CHCl_3$ (200 + 3 × 100 mL)

**Table 3** Spectroscopical Data for 2-Alkylpyrazole-*N*-oxides **2**, *N*-Alkyl-5-chloropyrazoles **3** and *N*-Alkyl-5-bromopyrazoles **4**

| Product | $^1H$ NMR (300 MHz, $CDCl_3$/TMS) δ, *J* (Hz) | $^{13}C$ NMR (75 MHz, $CDCl_3$/TMS), δ |
|---|---|---|
| **2a** | 3.81 (s, 3 H), 5.24 (s, 2 H), 6.11 (dd, 1 H, *J* = 3.9, 2.4), 6.77 (dd, 1 H, *J* = 3.9, 1.2), 6.90 (dd, 2 H, *J* = 7.2, 2.3), 7.22 (dd, 1 H, *J* = 2.4, 1.2), 7.30 (dd, 2 H, *J* = 7.2, 2.3) | 48.0, 55.0, 101.1, 114.3, 118.2, 119.1, 126.0, 130.0, 159.7 |
| **2c** | 4.78 (ddd, 2 H, *J* = 6.0, 1.5, 1.2), 5.25 (ddt, 1 H, *J* = 17.1, 1.0, 1.5), 5.34 (ddt, 1 H, *J* = 10.2, 1.0, 1.2), 5.95 (ddt, 1 H, *J* = 17.1, 10.2, 6.0), 6.17 (dd, 1 H, *J* = 3.9, 2.4), 6.99 (dd, 1 H, *J* = 3.9, 1.2), 7.21 (dd, 1 H, *J* = 2.4, 1.2) | 46.8, 101.0, 118.4, 119.0, 119.8, 130.3 |
| **2d**HBr[a] | 3.90 (s, 3 H), 6.65 (br dd, 1 H, *J* = 3.5, 2.8), 8.11 (br d, 1 H, *J* = 3.5), 8.27 (br dd, 1 H, *J* = 2.8, 1.2), 13.06 (br s, 1 H, exchangeable with $D_2O$) | |
| **2d** | 3.77 (s, 3 H), 6.12 (dd, 1 H, *J* = 3.7, 2.5), 6.97 (dd, 1 H, *J* = 3.7, 1.2), 7.17 (dd, 1 H, *J* = 2.5, 1.2) | 32.2, 101.1, 119.1, 119.4 |
| **2e** | 0.96 (t, 3 H, *J* = 7.4), 1.38 (m, 2 H), 1.83 (m, 2 H), 4.16 (t, 2 H, *J* = 7.2), 6.13 (dd, 1 H, *J* = 3.9, 2.4), 6.98 (dd, 1 H, *J* = 3.9, 1.2), 7.18 (dd, 1 H, *J* = 2.4, 1.2) | 13.2, 19.3, 30.3, 44.9, 100.8, 118.5, 119.0 |
| **2f** | 1.40 (d, 6 H, *J* = 6.9), 5.03 (sept, 1 H, *J* = 6.9), 6.10 (dd, 1 H, *J* = 3.9, 2.4), 6.90 (dd, 1 H, *J* = 3.9, 1.2), 7.14 (dd, 1 H, *J* = 2.4, 1.2) | 21.4, 47.1, 101.2, 115.1, 119.5 |
| **3a** | 3.77 (s, 3 H), 5.27 (s, 2 H), 6.21 (d, 1 H, *J* = 2.0), 6.85 (d, 2 H, *J* = 8.8), 7.20 (d, 2 H, *J* = 8.8), 7.51 (d, 1 H, *J* = 2.0) | 52.2, 55.2, 105.1, 114.1, 127.0, 128.1, 129.1, 139.5, 159.4 |
| **3c** | 4.75 (ddd, 2 H, *J* = 5.5, 1.7, 1.4), 5.10 (dtd, 1 H, *J* = 17.1, 1.7, 1.1), 5.25 (dtd, 1 H, *J* = 10.3, 1.4, 1.1), 5.96 (ddt, 1 H, *J* = 17.1, 10.3, 5.5), 6.21 (d, 1 H, *J* = 2.0), 7.50 (d, 1 H, *J* = 2.0) | 51.4, 104.8, 118.0, 127.0, 132.0, 139.5 |
| **4a** | 3.77 (s, 3 H), 5.30 (s, 2 H), 6.29 (d, 1 H, *J* = 1.9), 6.85 (dd, 2 H, *J* = 6.8, 2.2), 7.21 (dd, 2 H, *J* = 6.8, 2.2), 7.52 (d, 1 H, *J* = 1.9) | 53.3, 55.2, 108.8, 112.6, 114.1, 128.3, 129.0, 140.5, 159.4 |
| **4c** | 4.76 (ddd, 2 H, *J* = 5.5, 1.7, 1.4), 5.05 (dtd, 1 H, *J* = 17.1, 1.7, 1.1), 5.21 (dtd, 1 H, *J* = 10.3, 1.4, 1.1), 5.93 (ddt, 1 H, *J* = 17.1, 10.3, 5.5), 6.27 (d, 1 H, *J* = 1.9), 7.48 (d, 1 H, *J* = 1.9) | 52.5, 108.7, 112.7, 118.1, 132.1, 140.5 |
| **4d** | 3.87 (s, 3 H), 6.27 (d, 1 H, *J* = 1.9), 7.45 (d, 1 H, *J* = 1.9) | 37.4, 108.5, 113.1, 140.0 |

[a] $^1H$ NMR spectrum obtained in DMSO-$d_6$.

and the combined organic layers were washed with $H_2O$ (20 mL) and dried ($MgSO_4$). Evaporation produced analytically pure **2a** (32.2 g, 94%) as a thick syrup that solidified on standing; mp 48–50 °C (crude product); $R_f$ 0.36 (EtOAc–MeOH, 5:1).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found (crude product): C, 64.50; H, 6.01; N, 13.58.

**2-Benzylpyrazole-1-oxide (2b)**
This compound was prepared as described previously.[3]

**2-Allylpyrazole-1-oxide (2c)**
Compound **1** (244 mg, 2.90 mmol) and allyl bromide (1.3 mL, 15.0 mmol) were dissolved in $CHCl_3$ (4 mL) and stirred at 80 °C for 18 h in a screw-cap sealed vessel. The mixture was poured into toluene (5 mL) and extracted with 37% aq HCl (2 × 5 mL). The combined aqueous layers were basified to pH >10 with 33% aq NaOH solution while cooling in an ice bath. The aqueous layer was extracted with $CHCl_3$ (8 × 10 mL) and the combined organic layers were dried ($Na_2SO_4$) and evaporated to yield analytically pure **2c** as *very hygroscopic* crystals (311 mg, 86%); mp 36–38 °C (crude, sealed tube); $R_f$ 0.29 (EtOAc–MeOH, 5:1).

Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found (crude product): C, 57.77; H, 6.50; N, 22.41.

**2-Methylpyrazole-1-oxide (2d)**
Compound **1** (1.69 g, 20.1 mmol) was dissolved in $CHCl_3$ (20 mL). MeBr (10 mL, 210 mmol) was added and the mixture was stirred at 80 °C for 12 h in a screw-cap sealed vessel. The suspension was allowed to reach r.t., diluted with $Et_2O$ (40 mL) and filtered. The crystals were washed with $Et_2O$ and dried to yield analytically pure **2d**HBr (3.30 g, 92%); mp 120–120.5 °C (crude product).

Anal. Calcd for $C_4H_7BrN_2O$: C, 26.84; H, 3.94; N, 15.65; Br, 44.64. Found (crude product): C, 27.04; H, 3.68; N, 15.55; Br, 44.55.

**Liberation of 2d from its HBr-Salt**
The salt **2d**HBr (3.39 g, 18.9 mmol) was slowly added to aq 33% NaOH solution (10 mL) and the mixture was continously extracted with $Et_2O$ for 7 h using a Kutscher-Steudel apparatus. The $Et_2O$ layer was concentrated to approximately half the volume and diluted with $CH_2Cl_2$ (100 mL) to dissolve the glassy product formed in the etheral layer. $MgSO_4$ was added and the mixture filtered. Evaporation gave analytically pure **2d** (1.75 g, 94%) as hygroscopic crystals; mp (crude product, sealed tube) 69–71 °C. (Lit.[2] mp 65–69 °C); $R_f$ 0.11 (EtOAc–MeOH, 5:1).

Anal. Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.16; N 28.55. Found (crude product): C, 48.73; H, 6.40; N, 28.28.

**2-Butylpyrazole-1-oxide (2e)**
Compound **1** (260 mg, 3.09 mmol) and 1-bromobutane (2.51 g, 18 mmol) were dissolved in $CHCl_3$ (4 mL) and heated in a screw-cap sealed vessel at 100 °C for 24 h. The suspension was allowed to reach r.t. and was then poured into toluene (5 mL) and extracted with 37% aq HCl (2 × 5 mL). The combined aqeous layers were basified to pH >10 with 33% aq NaOH solution while cooling in an ice-bath and extracted with $CHCl_3$ (8 × 10 mL). The organic layer was dried ($Na_2SO_4$) and evaporated to dryness. FC (EtOAc → EtOAc–MeOH, 5:1) produced **2e** as an oil (213 mg, 49%); $R_f$ 0.24 (EtOAc–MeOH, 5:1).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.69; H, 8.35; N, 19.84.

**2-Isopropylpyrazole-1-oxide (2f)**
Compound **1** (244 mg, 2.90 mmol) and 2-bromopropane (1.5 mL, 16.0 mmol) were dissolved in $CHCl_3$ (4 mL) and heated to 100 °C for 40 h in a screw-cap sealed vessel. The suspension was allowed to reach r.t. and was then poured into 33% aq NaOH solution (10 mL) and continously extracted with $Et_2O$ overnight in a Kutschel–Steudel apparatus. Evaporation of $Et_2O$ extract produced 122 mg (33%) of **2f** as a *very hygroscopic* semi-crystalline compound; $R_f$ 0.25 (EtOAc–MeOH, 5:1).

Anal. Calcd for $C_6H_{10}N_2O18\%H_2O$: C, 55.69; H, 8.07; N, 21.65. Found (crude product): C, 55.94; H, 7.77; N, 21.22.

**1-Alkyl-5-halopyrazoles 3 and 4; General Procedure**
The 2-alkylpyrazole-1-oxides **2a-d** (2 mmol) were dissolved in $CHCl_3$ (7 mL) and cooled to 0 °C. A solution of $POX_3$ in $CHCl_3$ ($POCl_3$: 3.0 M; $POBr_3$: 1.2 M, 4–5 equiv) was added dropwise. After 20 min at 0 °C, the mixture was allowed to stir for 30 min at r.t. and then heated to 50 °C for 2 h 30 min under a positive pressure of $N_2$. Addition of $POX_3$ at r.t. or 50 °C produced a crude product of lower purity. The mixture was evaporated to dryness and the pH was adjusted to 7–8 by addition of sat. aq $NaHCO_3$ solution. The aqueous solution was extracted with $Et_2O$ (5 × 10 mL) and the combined organic layers were washed with $H_2O$, dried ($Na_2SO_4$), filtered through a plug of silica gel 60 H and evaporated to dryness.

5-Chloro-1-(4-methoxybenzyl)pyrazole (**3a**)
Thick oil (93%); $R_f$ 0.39 ($CHCl_3$).

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found (crude product): C, 59.04; H, 5.06; N, 12.34.

1-Benzyl-5-chloropyrazole (**3b**)
Oil (98%). Identical with an authentic sample.[12]

1-Allyl-5-chloropyrazole (**3c**)
Oil (83%); $R_f$ 0.67 (EtOAc–petroleum ether, 1:2). An analytically pure sample of **3c** was obtained by bulb-to-bulb distillation at 15 Torr (r.t.).

Anal. Calcd for $C_6H_7ClN_2$: C, 50.54; H, 4.95; N, 19.65. Found: C, 50.52; H, 5.08; N, 19.56.

5-Chloro-1-methylpyrazole (**3d**)
General procedure was followed except heating for 10 h; oil (70%). Identical with an authentic sample.[12]

5-Bromo-1-(4-methoxybenzyl)pyrazole (**4a**)
Crystals (95%); mp 45–47 °C (crude product); $R_f$ 0.63 (EtOAc–petroleum ether, 1:2). An analytical sample was recrystallized from petroleum ether.

Anal Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.68; H, 3.99; N, 10.35.

1-Benzyl-5-bromopyrazole (**4b**)
Oil (87%). Identical with an authentic sample.[1]

1-Allyl-5-bromopyrazole (**4c**)
Oil (85%); $R_f$ 0.69 (EtOAc–petroleum ether, 1:2). An analytically pure sample of **4c** was obtained by bulb-to-bulb distillation at 15 Torr (r.t.).

Anal. Calcd for $C_6H_7ClN_2$: C, 38.53; H, 3.77; N, 14.98. Found: C, 38.61; H, 3.84; N, 14.71.

5-Bromo-1-methylpyrazole (**4d**)
Oil (78%). An analytically pure sample of **4d** was obtained by bulb-to-bulb distillation at 15 Torr (r.t.).

Anal. Calcd. for $C_4H_5BrN_2$: C, 29.84; H, 3.13; N, 17.40. Found: C, 30.05; H, 3.07; N, 17.11.

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