Convergent Synthesis of 3-Arylated 1-Hydroxypyrazoles via 3-Metalated Pyrazole-1-oxides

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Pyrazoles possessing C-aryl substituents appear frequently in molecules of pharmaceutical interest, and a wide range of biological activities has been reported.[1] We have previously reported the preparation of 4-[2] and 5-substituted[3] 1-benzyloxypyrazoles employing C-4- and C-5-metalated intermediates generated from 1-benzyloxypyrazole by C-4 iodination and subsequent iodine−magnesium exchange or by direct C-5 lithiation. These methods have been extended to the preparation of 4-[2] and 5-arylated[4] 1-benzyloxypyrazoles via transmetalation with $ZnCl_2$ and Pd(0)-catalyzed cross-coupling. The substituted 1-benzyloxypyrazoles can be debenzylated by Pd/C-catalyzed hydrogenolysis or by treatment with aqueous acid furnishing 4- and 5-substituted 1-hydroxypyrazoles. While these methodologies smoothly introduce substituents in the 4- and 5-positions, they are incapable of accessing the 3-position since metalation at the C-3 position of 1-substituted pyrazoles[5] is hampered by the adjacent lone pair effect.[6] In addition, no direct approach to 3-halogen-substituted pyrazoles exists due to preferential electrophilic attack at C-4 of 1-substituted pyrazoles.[7]

We now wish to report a convergent preparation of novel 3-arylated 1-hydroxypyrazoles (**5a**−**g**).[8] The sequence is based on formation of the 2-(4-methoxybenzyl)-pyrazole-1-oxide (**2**), which undergoes selective monobromination at C-3 and subsequent bromine−magnesium exchange, transmetalation with $ZnCl_2$, Negishi-type cross-coupling, and finally acid-induced deparamethoxybenzylation.

Traditionally, 2-alkylpyrazole-1-oxides have been prepared by tedious peracid oxidation of the corresponding 1-alkylpyrazoles.[9,10] Recently, we described the synthesis of 2-alkylpyrazole-1-oxides by heating **1** at 60−100 °C with alkylbromides in $CHCl_3$.[11] The elevated temperatures required indicated an S_N1-type substitution reaction mechanism. The deparamethoxybenzylation of the 2-PMB-pyrazole-1-oxides **4a**−**g** also indicated a cationic pathway (vide infra). On this basis, we decided to design a new reaction for the selective N-alkylation of **1** based on capture of benzylic cations generated from 4-methoxybenzyl alcohol (PMB-OH) in an acidic environment, thus avoiding the use of the carcinogenic[12] and unstable[13] PMB-Br.

Indeed, treatment of **1** and PMB-OH with TFA in $CHCl_3$ gave the desired 2-PMB-pyrazole-1-oxide in 94% yield (Scheme 1).

In line with this result, benzhydrol, another carbinol capable of giving relatively stabilized carbocations, gave 2-benzhydrylpyrazole-1-oxide in 96% yield when subjected to the same conditions.

In contrast to 1-alkoxypyrazoles, 2-alkylpyrazole-1-oxides are activated toward electrophilic attack at the C-3 position.[9,14] Thus, 2-benzylpyrazole-1-oxide was exclusively brominated at the C-3 position.[9] Similarly, bromine was smoothly introduced at the C-3 position of **2** providing **3** in 94% yield (Scheme 1).

Bromine−magnesium exchange has previously been shown to be an efficient way of generating aryl and heteroarylmagnesium species.[15] Gratifyingly, **3** was converted to the corresponding magnesium species upon treatment with isopropylmagnesium chloride (*i*-PrMgCl) in THF at −78 °C for 15 min.[16]

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Scheme 1

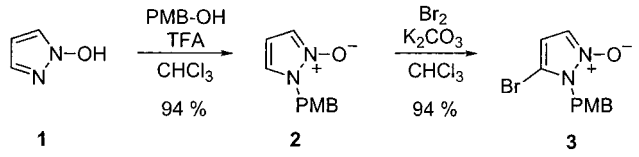
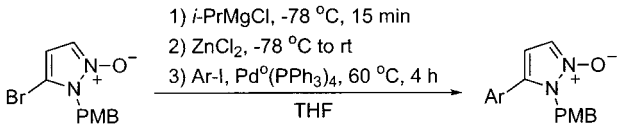


Table 1. Preparation of 3-Aryl- and 3-Heteroaryl-substituted 2-PMB-Pyrazole-1-oxides



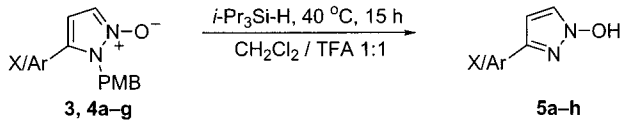
entry	Ar	product	yield (%)[a]
1	4-MeO-Ph	**4a**	72
2	4-NO_2-Ph	**4b**	79
3	4-Me-Ph	**4c**	81
4	2-NO_2-Ph	**4d**	74
5	2-F-Ph	**4e**	62
6	2-Pyridyl[b]	**4f**	81
7	2-Thienyl	**4g**	79

[a] Isolated yields of analytically pure compounds. [b] 2-Bromopyridine was used.

Combining the regioselective bromination, the bromine−magnesium exchange, and the transmetalation with $ZnCl_2$ followed by palladium(0)-catalyzed cross-coupling,[17] we synthesized a series of 3-arylated and 3-heteroarylated 2-PMB-pyrazole-1-oxides (**4a**−**g**) in good yields (Table 1). Attempts to reverse the polarity of the reaction by performing a Suzuki−Miyaura-type cross-coupling[18] of 4-methoxyphenylboronic acid and **3** produced **4a** in only 51% yield, mainly due to reduction of **3** to **2**.

PMB groups can be removed from sp^2-hybridized nitrogens in highly acidic media, but yields are generally very substrate dependent.[19] Attempts to remove the PMB group from 3-aryl-substituted pyrazole-1-oxides such as **4a** and **4c** in strong mineral acids (e.g., 37% HCl, 47% HBr, or concentrated H_2SO_4) produced intractable and complex reaction mixtures in which byproducts, originating from electrophilic substitution of PMB cations into the C-3 aryl group, could be detected. Performing the deparamethoxybenzylation in TFA/CH_2Cl_2 solution with trapping of the PMB cations by triisopropylsilane afforded the 3-substituted 1-hydroxypyrazoles **5a**−**h** cleanly and in high yields (Table 2).

Table 2. Deparamethoxybenzylation of 3-Substituted 2-PMB-Pyrazole-1-oxides



entry	substrate	X/Ar	product	yield (%)[a]
1	**4a**	4-MeO-Ph	**5a**	74
2	**4b**	4-NO_2-Ph	**5b**	80
3	**4c**	4-Me-Ph	**5c**	92
4	**4d**	2-NO_2-Ph	**5d**	80
5	**4e**	2-F-Ph	**5e**	71
6	**4f**	2-Pyridyl	**5f**	96[b]
7	**4g**	2-Thienyl	**5g**	89
8	**3**	Br	**5h**	72

[a] Isolated yields of analytically pure compounds. [b] Isolated as HCl salt.

Thus, 2-PMB-pyrazole-1-oxides are both produced and deparamethoxybenzylated in chlorinated solvents containing TFA. The presence or lack of the triisopropylsilane as a cation scavenger, together with the amount of TFA present in the reaction mixture, controls the direction of the reaction.

The procedure described herein allows for the preparation of 3-substituted 1-hydroxypyrazoles via bromine−magnesium exchange of 3-bromo-2-PMB-pyrazole-1-oxide (**3**) obtained in two steps from **1**.

The transformation of 1-hydroxypyrazole (**1**) to the corresponding pyrazole-1-oxide **2** and subsequent C-3 functionalization represent a novel approach for alternating the regioselectivity to generate otherwise inaccessible substitution patterns with potential use for pharmaceutical and agrochemical applications. This mode of activation−functionalization is currently being investigated for implementation in other heterocyclic *N*-oxides.

Experimental Section

General. All reactions were performed under N_2 using syringe−septum cap techniques. All glassware was flame-dried prior to use. Flash chromatography was performed using Merck 60 (230−400 mesh) silica gel. Melting points are uncorrected. NMR spectra were recorded on a Varian instrument with TMS as the internal standard at 300−75 MHz and performed at 20 °C unless otherwise stated. Solvents and reagents were obtained from Fluka or Aldrich and used without further purification. THF was freshly distilled from Na/benzophenone ketyl under N_2. A 1.0 M solution of $ZnCl_2$ was prepared by flame-drying the zinc salt in vacuo before it was dissolved in THF. *i*-PrMgCl was titrated prior to use.[20] $Pd(PPh_3)_4$ was prepared as previously described.[21]

2-(4-Methoxybenzyl)pyrazole-1-oxide (2). 4-Methoxybenzyl alcohol (1.02 g, 7.41 mmol) and 1-hydroxypyrazole[22] (346 mg, 4.12 mmol) were dissolved in dry $CHCl_3$ (10 mL) before TFA (0.95 mL, 12.4 mmol) was added dropwise. The mixture was heated to 50 °C for 25 h. After cooling to room temperature, the mixture was poured into toluene (20 mL) and extracted with 37% HCl (4 × 10 mL). The combined aqueous layers were washed with toluene (5 mL) and cautiously basified with 33% NaOH to pH > 10 while cooling in an ice−water bath. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL), and the combined organic layers were washed with water (10 mL) and dried over $MgSO_4$. Evaporation gave analytically pure 2-(4-methoxybenzyl)pyrazole-1-oxide (793 mg, 94%) as a clear syrup

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that solidified upon standing. Mp: 48−50 °C. R_f = 0.30 (5:1 EtOAc/MeOH). ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 3H), 5.24 (s, 2H), 6.05 (dd, 1H, J = 3.9, 2.4 Hz), 6.72 (dd, 1H, J = 3.9, 1.2 Hz), 6.87 (d, 2H, J_{app}[23] = 8.7 Hz), 7.16 (dd, 1H, J = 2.4, 1.2 Hz), 7.22 (d, 2H, J_{app} = 8.7 Hz). ^{13}C NMR ($CDCl_3$): δ 48.0, 55.0, 101.1, 114.3, 118.2, 119.1, 126.0, 130.0, 159.7. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.50; H, 6.01; N, 13.58.

3-Bromo-2-(4-methoxybenzyl)pyrazole-1-oxide (3). 2-(4-Methoxybenzyl)pyrazole-1-oxide (**2**) (8.66 g, 42.4 mmol) was dissolved in $CHCl_3$ (120 mL), and freshly mortared anhydrous K_2CO_3 (16.8 g, 122 mmol) was added. The suspension was cooled to −55 °C in the dark before addition of neat bromine (2.30 mL, 44.8 mmol) over 10 min at between −55 and −50 °C. Stirring was continued for 30 min before the cooling bath was removed. The mixture was subsequently stirred at room temperature for 1 h. The orange mixture was decolorized by addition of a minimum amount of 1 M aqueous Na_2SO_3. CH_2Cl_2 (25 mL) and water (20 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated to yield off-white crystals. After washings with cold (approximately 0 °C) diethyl ether (50 mL), 3-bromo-2-(4-methoxybenzyl)pyrazole-1-oxide (**3**) was obtained as colorless crystals (11.3 g, 94%). Mp: 103−104 °C. R_f = 0.42 (10:1 EtOAc/MeOH). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 5.37 (s, 2H), 6.20 (d, 1H, J = 2.4 Hz), 6.85 (d, 2H, J_{app} = 9.0 Hz), 7.18 (d, 1H, J = 2.4 Hz), 7.36 (d, 2H, J_{app} = 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ 46.8, 55.2, 99.5, 104.4, 114.1, 119.9, 126.5, 129.8, 159.6. Anal. Calcd for $C_{11}H_{11}N_2O_2Br$: C, 46.67; H, 3.92; N, 9.89. Found: C, 46.40; H, 3.97; N, 9.68.

Representative Procedure for Arylation of 3-Bromo-2-PMB-pyrazole-1-oxide (3): Preparation of 3-(4-Methylphenyl)-2-(4-methoxybenzyl)pyrazole-1-oxide (4c). 3-Bromo-2-(4-methoxybenzyl)pyrazole-1-oxide (**3**) (293 mg, 1.03 mmol) was dissolved in THF (10 mL) and cooled to −78 °C before *i*-PrMgCl (2.1 M, 0.60 mL, 1.26 mmol) was added dropwise causing precipitation. After 15 min, $ZnCl_2$ (1 M in THF, 3.0 mL, 3.0 mmol) was added, and the suspension was stirred at −78 °C for 10 min and at room temperature for 20 min before the aryl iodide (2.06 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.029 mmol) were added neat. The mixture was heated to 60 °C for 4 h, and the reaction was quenched with saturated NH_4Cl (10 mL). Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), and the solvents were evaporated. Flash chromatography (EtOAc → 10:1 EtOAc/MeOH) on silica gel gave the title compound as colorless crystals. Yield: 81%. Mp: 88−90 °C (EtOAc/heptane). R_f = 0.55 (5:1 EtOAc/MeOH). ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 3.76 (s, 3H), 5.36 (s, 2H), 6.16 (d, 1H, J = 2.4 Hz), 6.80 (d, 2H, J_{app} = 8.7 Hz), 7.07 (d, 2H, J_{app} = 8.7 Hz), 7.16−7.23 (m, 4H), 7.29 (d, 1H, J = 2,4 Hz). ^{13}C NMR ($CDCl_3$): δ 21.1, 46.3, 55.0, 100.5, 114.0, 119.4, 126.4, 127.9, 128.3, 128.6, 129.6, 134.0, 139.1, 159.1. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.16; H, 6.10, N, 9.70.

Representative Procedure for Deparamethoxybenzylation of 3-Arylated 2-PMB-Pyrazole-1-oxides: Preparation of 3-(4-Methylphenyl)-1-hydroxypyrazole (5c). To a solution of 3-(4-methylphenyl)-2-(4-methoxybenzyl)pyrazole-1-oxide (**4c**) (321 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) was added triisopropylsilane (0.54 mL, 2.63 mmol). After slow addition of TFA (10 mL), the mixture was gently refluxed until the starting compound was completely converted as indicated by TLC (approximately 15 h). The mixture was evaporated to dryness, and the resulting white crystalline mass was partitioned between water (10 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by flash chromatography (petroleum ether → 1:1 petroleum ether/EtOAc) on silica gel to give 174 mg (92%) of **5c** as colorless crystals. Mp: 180−181 °C. R_f = 0.21 (1:1 heptane/EtOAc). ^{1}H NMR (DMSO-d_6, 40 °C):[24] δ 2.30 (s, 3H), 6.57 (d, 1H, J = 2.3 Hz), 7.19 (d, 2H, J_{app} = 7.9 Hz), 7.58 (d, 1H, J = 2.3 Hz), 7.63 (d, 2H, J_{app} = 7.9 Hz). ^{13}C NMR (DMSO-d_6): δ 20.7, 99.9, 124.3, 124.6, 129.3, 130.7, 136.4, 143.2. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.23; H, 5.76; N, 15.88.

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Supporting Information Available: Experimental details and spectral data for all compounds mentioned above. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For clarity, the coupling patterns are reported as they appear. Thus, the AA′XX′ coupling patterns observed in, for example, the 4-methoxybenzyl group are reported as $J_{app} = J_{AX} + J_{AX'}$.

(24) The chemical shifts for H-4 and H-5 in the pyrazole moiety were slightly temperature dependent.