Synthesis of 5-Substituted 1-Hydroxypyrazoles through Directed Lithiation of 1-(Benzyloxy)pyrazole

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1-Hydroxypyrazoles have been converted to 1-(benzyloxy), [(9-phenylfluorenyl)oxy], [(*N*,*N*-diethylcarbamoyl)oxy], and (silyloxy)pyrazoles. 1-(Benzyloxy)pyrazole was lithiated selectively in the 5-position. Subsequent reaction with electrophiles gives rise to 1-(benzyloxy)pyrazole with carbon, halogen, silicon, sulfur, or tin substituents at the 5-position. 1-(Benzyloxy)pyrazoles could be debenzylated by hydrogen bromide or hydrogenolysis producing 5-substituted 1-hydroxypyrazoles in high overall yield.

Introduction

Electrophiles have been introduced in a regiospecific manner into the nucleus of 1-alkyl- and 1-phenylpyrazoles by metalation followed by reaction of the generated anion with an electrophile.[1–6] See ref 7 for a review. This approach has now been used to introduce a wide variety of substituents into the 5-position of 1-hydroxypyrazole (**1**). Such *N*-hydroxyazoles might be of great interest as intermediates in the synthesis of substituted azoles, as auxiliaries in mixed anhydride catalyzed condensations,[8–10] and as possible metabolites in the biological degradation of azoles.

1-Hydroxypyrazole (**1**) can be prepared by pyrolysis of azoxyoxaazatricyclodecadienes,[11] by direct oxidation of pyrazole with peroxyphthalic acid and base,[12] with dibenzoyl peroxide and base,[13] or with 3-chloroperbenzoic acid.[14] The oxygen at the nucleus is expected to exert a stabilizing effect on an adjacent carbanion if a lithium cation acts as a link in the coordination. This explains why a series of oxygen- and nitrogen-containing substituents display an *ortho*-directing effect.[15] In reported examples *ortho*-directing groups have usually been situated at ring carbon atoms. However, a protected *N*-hydroxy function has been used as an *ortho*-directing group in the indole series.[16]

In the present study, a series of groups for protection of the oxygen atom and directing the metalation of 1-hydroxypyrazole (**1**) was examined in order to find a suitable one which can be regioselectively introduced, withstand the reaction conditions, and then be removed selectively under mild conditions.

Results and Discussion

Protection. 1-Hydroxypyrazoles protected at the oxygen atom **2a-e** were readily prepared in good to excellent yield by reacting 1-hydroxypyrazole (**1**) with benzyl bromide, 9-bromo-9-phenylfluorene, *N*,*N*-diethylcarbamoyl chloride, *tert*-butyldimethylsilyl chloride, or *tert*-butyldiphenylsilyl chloride (Scheme 1). The reactions were performed in dichloromethane using *N*-ethyldiisopropylamine. In these reactions competing attack at N-2 to give pyrazole *N*-oxides was considered.[17] However, NMR spectra revealed *O*-protected products **2a-e** to be the single products since the position at 80 ppm of the CH_2 carbon signal of **1a** is characteristic of oxygen-substituted carbon atoms. In contrast, the NCH_2 signal of the isomeric 2-benzylpyrazole 1-oxide resonates at 48 ppm.[17] Furthermore, C-3 of **2a-e**, like other 1-substituted pyrazoles, resonates at *ca.* 132 ppm[18] while C-3 of pyrazole 1-oxides resonates at *ca.* 119 ppm.[17] Finally, $J_{H\text{-}3,H\text{-}4}$ in **2a-e**, like in other 1-substituted pyrazoles,[19] is *ca.* 2.3 Hz while the corresponding coupling in pyrazole *N*-oxides is *ca.* 3.9 Hz.[17]

The *O*-protected 1-hydroxypyrazoles **2a-e** were purified by flash chromatography. Distillation was avoided as other *N*-alkoxypyrazoles have been reported to explode.[20] The lower yield of the silylated 1-hydroxypyrazoles **2b,c** may be attributed to partial hydrolysis during the chromatographic separation.

Lithiation. Lithiation of [(*N*,*N*-diethylcarbamoyl)oxy]-pyrazole **2d** and subsequent quenching with D_2O resulted in quantitative incorporation of deuterium at C-5 in 70% yield. The position of the deuterium incorporation was proven as described below.

Lithiation of 1-(benzyloxy)pyrazole (**2a**) with n-BuLi in THF with TMEDA as the catalyst at −78 °C for 5 min followed by addition of D_2O afforded the expected 5-deuterio compound **4a** (100% deuterium incorporation) in

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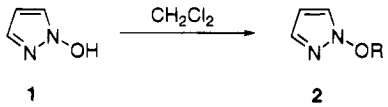
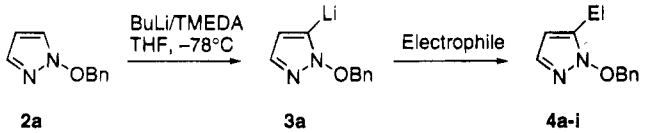
Scheme 1



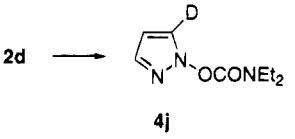
1 2

	R	Yield (%)
a	Bn	99
b	SiBu^{t}Ph$_2$	77
c	SiBu^{t}Me$_2$	66
d	CONEt$_2$	97
e	9-Ph-fluorenyl	73

Scheme 2



2a 3a 4a-i



4j

	El	Electrophile	Yield (%)
a	D	D_2O	97
b	Me	MeI	95
c	CHO	DMF	93
d	Cl	C_2Cl_6	79
e	Br	CBr_4	83
e	Br	Br_2	87
f	I	I_2	94
g	$SiMe_3$	Me_3SiCl	87
h	$SnBu_3$	Bu_3SnCl	90
i	SMe	Me_2S_2	95

97% isolated yield (see Scheme 2). The position of the deuteration was proved as described below. It is noteworthy that no lithiation at the benzyl CH_2 group of compound **2a** was observed under these conditions. This is in contrast to the lithiation of 1-benzylpyrazole in the presence of TMEDA which under kinetic control takes place exclusively at the CH_2 group.[21] The position of the deuteration of compounds **4a** and **4j** was determined using ^1H and ^{13}C NMR spectroscopy. In the proton spectra, the C-5 proton signals at 6.97 ppm of **2a** and 7.39 ppm of **2d** disappear. In the carbon spectra, the C-5 signal of compound **4a** at 122.4 ppm and 124.3 ppm of **4j** were converted to triplets, characteristic of a deuterio-substituted carbon atom. The assignment of the signals from C-3 (133.2 ppm) and C-5 (122.4 ppm) in 1-(benzyloxy)pyrazole (**2a**) is in agreement with the relative position of these signals in 1-alkyl- and 1-aryl-substituted pyrazoles.[18] The assignment is confirmed by the coupling constants since $^3J_{C\text{-}3,H\text{-}5}$ is larger than $^2J_{C\text{-}3,H\text{-}4}$ and $^2J_{C\text{-}5,H\text{-}4}$ is larger than $^3J_{C\text{-}5,H\text{-}3}$ as observed in 1-alkyl- and 1-aryl-substituted pyrazoles.[18,22]

Reaction with Electrophiles. The utility of the lithiation in synthesis of 5-substituted pyrazoles was demonstrated by the reaction of the 1-(benzyloxy)-5-lithiopyrazole (**3a**) with carbon, halogen, sulfur, silicon, and tin electrophiles to give a wide variety of 5-substituted 1-(benzyloxy)pyrazoles **4a-i** in good to excellent yields.

When the electrophile was dimethylformamide, quenching with dilute acid produced the formyl compound **4c**. While this method has been used extensively to formylate imidazoles,[23] only an attempt to formylate [[1-(trimethylsilyl)ethoxy]methyl](SEM)-pyrazoles, which proved unsuccessful, has been reported for the pyrazole series.[2]

In lithiation experiments, the *tert*-butyldiphenylsilyl protecting group was found to migrate. Thus, treatment of 1-[(*tert*-butyldiphenylsilyl)oxy]pyrazole (**2b**) with n-BuLi in THF with TMEDA at −78 °C followed by addition of trimethylsilyl chloride did not produce the desired 5-(trimethylsilyl)-1-[(*tert*-butyldiphenylsilyl)oxy]-pyrazole (Scheme 3). Instead, the isomeric compound **6a** was isolated in 99% yield. The formation of **6a** is most likely due to migration of the *tert*-butyldiphenylsilyl group of the anion **3b** from oxygen to C-5. The O−Si bond is stronger than the C−Si bond[24] but this difference may be overwhelmed by the difference between the strength of the O−Li bond and the C−Li bond making **5** thermodynamically more stable than **3b**. A related *N* → *C* migration of silyl groups was observed by lithiation of 1-(*tert*-butyldimethylsilyl)pyrazoles.[4]

Deprotection. The benzyl group of the 5-substituted 1-(benzyloxy)pyrazoles could be removed readily by mild hydrogenolysis (10% Pd/C at 0 °C) or by treatment with 47% aqueous hydrogen bromide as shown for the compounds **2a**, **4d**, and **4g** which produced the corresponding 1-hydroxypyrazoles **1**, **6b**, and **6c** in almost quantitative yield (Scheme 4).

The experiments above demonstrate that 5-substituted 1-(benzyloxy)pyrazoles **4a-i** can be prepared in excellent yields by lithiation of 1-(benzyloxy)pyrazole **2a** with n-BuLi/TMEDA and subsequent reaction with various electrophiles. The *N*-(benzyloxy) group appears to be excellent for directed metalation stabilizing the intermediate pyrazol-5-yllithium **3** species. As demonstrated for compound **2a**, **4d**, and **4g** the benzyl protecting group can be removed under mild conditions, thus providing ready access to 5-substituted 1-hydroxypyrazoles **6**. Hence, regio- and monoselective introduction of electrophiles in the 5-position of 1-hydroxypyrazoles can be achieved by rational use of activating groups.

Experimental Section

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen using syringe−septum cap techniques. All glassware was flame-dried prior to use. Flash chromatography[25] was performed using silica gel Merck 60 (70−230 mesh). Melting points are uncorrected. All new compounds were colorless, unless otherwise stated. NMR spectra were recorded on a 200 MHz instrument as described in ref 14.

Materials. All solvents and reagents were obtained from Fluka or Aldrich and used without further purification with the following exceptions: THF was distilled from Na/benzophenone ketyl under nitrogen prior to use. CH_2Cl_2 and TMEDA were distilled from CaH_2 under nitrogen. *n*-Butyllithium was titrated prior to use.[26] Trimethylsilyl chloride was freshly distilled from calcium hydride. DMF was distilled from phosphorus pentoxide and stored over 3 Å molecular sieves.[27]

Protection. 1-(Benzyloxy)pyrazole (2a). To a solution of 1-hydroxypyrazole (**1**)[14] (1.68 g, 20 mmol) and *N*-ethyldiisopropylamine (3.6 mL, 21 mmol) in 20 mL of dry CH_2Cl_2 at 0 °C was added 2.50 mL of benzyl bromide. Stirring was continued at rt for 16 h. Removal of CH_2Cl_2 and flash chromatography (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:20 → 1:1:8) provided 3.43 g (99%) of 1-(benzyloxy)pyrazole (**2a**) as an oil: R_f (CH_2Cl_2−Et_2O−heptane 1:1:8) 0.23; ^1H-NMR ($CDCl_3$) δ 7.40−7.29 (m, 5H), 7.27 (dd, J = 2.3, 1.0 Hz, 1H), 6.97 (dd, J = 2.3, 1.0 Hz, 1H), 6.03 (t, J = 2.3 Hz, 1H), 5.27 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 133.7 (s), 133.2 (ddd, $J_{C\text{-}3,H\text{-}3}$ = 188.6,

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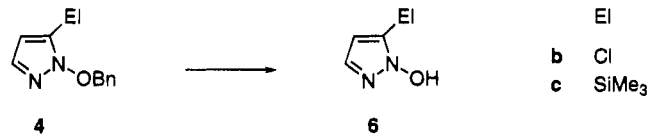
Scheme 3

2b **3b** **5** **6a** (99%)

Scheme 4



4 **6**

$J_{C\text{-}3,H\text{-}4}$ = 4.6, $J_{C\text{-}3,H\text{-}5}$ = 9.1 Hz, C−3), 129.4 (d), 129.0 (d), 128.4 (d), 122.4 (ddd, $J_{C\text{-}5,H\text{-}5}$ = 192.7, $J_{C\text{-}5,H\text{-}4}$ = 9.1, $J_{C\text{-}5,H\text{-}3}$ = 3.8 Hz, C−5), 102.9 (ddd, $J_{C\text{-}4,H\text{-}4}$ = 178.4, $J_{C\text{-}4,H\text{-}5}$ and $J_{C\text{-}4,H\text{-}3}$ 8.6 and 8.0 Hz, C−4), 80.2 (t). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.80; H, 5.80; N, 15.87.

1-[(*tert*-Butyldiphenylsilyl)oxy]pyrazole (2b). Similar reaction with *tert*-butyldiphenylsilyl chloride (5.40 mL, 21 mmol) followed by flash chromatography[28] (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:20 → 1:1:15) produced 4.99 g (77%) of 1-[(*tert*-butyldiphenylsilyl)oxy]pyrazole (**2b**): mp 39 °C (pentane); R_f (CH_2Cl_2−Et_2O−heptane 1:1:8) 0.50; ^{1}H-NMR ($CDCl_3$) δ 7.74−7.69 (m, 4H), 7.50−7.32 (m, 6H), 7.02 (dd, J = 2.3, 1.0 Hz, 1H), 6.91 (dd, J = 2.3, 1.0 Hz, 1H), 5.92 (t, J = 2.3 Hz, 1H), 1.18 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 135.7 (d), 131.4 (d), 130.7 (s), 130.4 (d), 127.7 (d), 121.5 (d), 102.9 (d), 26.5 (q), 19.2 (s). Anal. Calcd for $C_{19}H_{22}N_2OSi$: C, 70.77; H, 6.88; N, 8.69. Found: C, 70.86; H, 7.00; N, 8.56.

1-[(*tert*-Butyldimethylsilyl)oxy]pyrazole (2c). Similar reaction with *tert*-butyldimethylsilyl chloride (3.13 g, 21 mmol), followed by flash chromatography[29] (gradient elution: CH_2Cl_2−Et_2O−pentane 1:1:20 → 1:1:10), gave 2.61 g (66%) 1-[(*tert*-butyldimethylsilyl)oxy]pyrazole (**2c**) as an oil: R_f (CH_2Cl_2−Et_2O−pentane 1:1:15) 0.73; ^{1}H-NMR ($CDCl_3$) δ 7.17 (dd, J = 2.3, 1.1 Hz, 1H), 7.16 (dd, J = 2.4, 1.1 Hz, 1H), 6.14 (t, J = 2.3 Hz, 1H), 1.00 (s, 9H), 0.24 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 131.8 (d), 121.3 (d), 102.9 (d), 25.4 (q), 17.7 (s), −5.34 (q). Anal. Calcd for $C_9H_{18}N_2OSi$: C, 54.50; H, 9.15; N, 14.12. Found: C, 54.48; H, 9.33; N, 14.16.

1-[(*N*,*N*-Diethylcarbamoyl)oxy]pyrazole (2d). Similar reaction with *N*,*N*-diethylcarbamoyl chloride (2.79 mL, 22 mmol), followed by flash chromatography (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:20 → 1:1:2), afforded 3.55 g (97%) of 1-[(*N*,*N*-diethylcarbamoyl)oxy]pyrazole (**2d**) as an oil: R_f (CH_2Cl_2−Et_2O−heptane 1:1:2) 0.34; ^{1}H-NMR ($CDCl_3$) δ 7.39 (dd, J = 2.5, 1.0 Hz, 1H), 7.36 (dd, J = 2.3, 1.0 Hz, 1H), 6.30 (t, J = 2.4 Hz, 1H), 3.46 (q, J = 7.2 Hz, 2H), 3.38 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 152.8 (s), 133.8 (d), 124.3 (d), 104.2 (d), 43.2 (t), 41.7 (t), 13.9 (q), 12.8 (q). Anal. Calcd for $C_7H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.61; H, 7.19; N, 22.79.

1-(9-Phenylfluoren-9-yloxy)pyrazole (2e). Using the same procedure, but with 9-bromo-9-phenylfluorene (6.51 g, 20.3 mmol) as the alkylating agent, 4.72 g (73%) of crystalline 1-(9-phenylfluoren-9-yloxy)pyrazole (**2e**) was obtained after flash chromatography (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:20 → 1:1:8): mp 114 °C. An analytical sample of **2e** melting at 118−120 °C was obtained by low temperature recrystallization (EtOAc/heptane). Residual EtOAc was removed azeotropically with CH_2Cl_2: R_f (CH_2Cl_2−Et_2O−heptane 1:1:6) 0.34; ^{1}H-NMR ($CDCl_3$) δ 7.60−7.22 (m, 13H), 6.88 (dd, J = 2.3, 1.0 Hz, 1H), 6.58 (dd, J = 2.4, 1.0 Hz, 1H), 5.73 (t, J = 2.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 144.0, 140.9, 139.3, 131.9, 129.9, 128.3, 128.1, 127.9, 126.6, 126.0, 124.0, 119.8, 102.3, 97.0. Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.44; H, 5.09; N, 8.40.

(28) The compound is slightly unstable on silica gel.
(29) Some desilylation takes places during flash chromatography.

Lithiation of 1-(Benzyloxy)pyrazole (2a) followed by Reaction with an Electrophile. General. To a solution of 174 mg (1 mmol) of 1-(benzyloxy)pyrazole (**2a**) and 0.17 mL of TMEDA in 6 mL of dry THF with stirring at −78 °C was added dropwise 0.69 mL (1.1 mmol) of *n*-BuLi (1.6 M in hexane). After 5 min, the electrophile was added. Stirring was continued for 1 h, and the solution was allowed to warm to rt over 1 h and stirred for a further 1 h before workup by distribution of the crude product between CH_2Cl_2 (10 mL) and saturated NH_4Cl (10 mL), separation of the organic layer, extraction of the aqueous phase with CH_2Cl_2, drying of the organic layer (Na_2SO_4), filtration, and evaporation of the filtrate *in vacuo* at or below 40 °C in a rotary evaporator.

1-(Benzyloxy)-5-[^{2}H]pyrazole (4a). Using the general procedure, lithiation was followed by quenching with deuterium oxide (0.10 mL, 5.6 mmol) and worked up to give a crude product which by flash chromatography (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:20 → 1:1:8) provided 169 mg (97%) of 1-(benzyloxy)-5-[^{2}H]pyrazole (**4a**) as an oil. The ^{1}H NMR spectrum was identical with that of the starting material **2a** except that the signal at 6.97 ppm was absent, indicating quantitative deuteration at the 5-position.

1-(Benzyloxy)-5-methylpyrazole (4b). Using the general method, with methyl iodide (0.30 mL, 4.8 mmol) as the electrophile, followed by workup and flash chromatography (gradient elution: CH_2Cl_2−Et_2O−pentane 1:1:20 → 1:1:8) provided 179 mg (95%) of 1-(benzyloxy)-5-methylpyrazole (**4b**) as an oil. An analytical sample of **4b** was obtained by ball tube distillation at 0.02 mmHg (oven temperature 40 °C): R_f (CH_2Cl_2−Et_2O−pentane 1:1:10) 0.41; ^{1}H-NMR ($CDCl_3$) δ 7.37−7.24 (m, 5H), 7.20 (d, J = 2.2 Hz, 1H), 5.82 (dq, J = 2.2, 0.7 Hz, 1H), 5.25 (s, 2H), 1.85 (d, J = 0.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 133.7 (s), 132.4 (d), 132.1 (s), 129.8 (d), 129.1 (d), 128.4 (d), 102.2 (d), 79.6 (t), 9.1 (q). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.46; H, 6.57; N, 14.50.

1-(Benzyloxy)-5-formylpyrazole (4c). The general method was used with DMF (0.39 mL, 5 mmol) as the electrophile. The mixture was then stirred for 16 h with 5 mL of 2 M HCl and worked up by separation of the organic layer and extraction of the aqueous layer with CH_2Cl_2. The combined organic phases were dried and evaporated to dryness. Flash chromatography (gradient elution: CH_2Cl_2−Et_2O−pentane 1:1:20 → 1:1:8) provided 188 mg (93%) of 1-(benzyloxy)-5-formylpyrazole (**4c**), mp 43 °C. Recrystallization (EtOAc/pentane) gave mp 44 °C: R_f (CH_2Cl_2−Et_2O−pentane 1:1:6) 0.59; ^{1}H-NMR ($CDCl_3$) δ 9.47 (s, 1H), 7.40−7.22 (m, 6H), 6.65 (d, J = 2.5 Hz, 1H), 5.40 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 178.1 (d), 133.8 (s), 133.2 (d), 132.4 (s), 129.9 (d), 129.8 (d), 128.7 (d), 106.4 (d), 81.3 (t). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.5; H, 5.07; N, 13.64.

1-(Benzyloxy)-5-bromopyrazole (4e). Method a. To a solution of 174 mg of 1-(benzyloxy)pyrazole (**2a**) and 0.17 mL of TMEDA in 6 mL of dry THF with stirring at −78 °C was added dropwise 0.69 mL (1.1 mmol) of *n*-BuLi (1.6 M in hexane). After 5 min, bromine (106 μL, 2 mmol) was added. The orange solution was stirred at −78 °C for 1 h. Addition of $NaHSO_3$ (1.1 g) dissolved in 5 mL of MeOH−H_2O (1:1) resulted in a clear solution. Normal workup and flash chromatography (gradient elution: CH_2Cl_2−Et_2O−heptane 1:1:10 → 1:1:4) provided 11 mg (3%) 1-(benzyloxy)-4,5-dibromopyrazole: mp 53 °C; R_f (CH_2Cl_2−Et_2O−heptane 1:1:6) 0.61; ^{1}H-NMR ($CDCl_3$) δ 7.40 (br s, 5H), 7.36 (s, 1H), 5.29 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 134.3 (d), 132.5 (s), 129.9 (d), 129.6 (d), 128.6 (d), 108.8 (s), 94.4 (s), 81.1 (t). The next fraction contained 220 mg (87%) of 1-(benzyloxy)-5-bromopyrazole (**4e**) as an oil.

An analytical sample of **4e** was obtained by ball tube distillation at 0.02 mmHg (oven temperature 60 °C): R_f (CH_2Cl_2–Et_2O–heptane 1:1:6) 0.47; ^{1}H-NMR ($CDCl_3$) δ 7.42–7.33 (m, 5H), 7.29 (d, J = 2.4 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 5.27 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 134.1 (d), 132.8 (s), 129.8 (d), 129.2 (d), 128.4 (d), 106.3 (s), 106.2 (d), 80.7 (t). Anal. Calcd for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.51; H, 3.64; N, 11.14.

Method b. Alternatively, **4e** was prepared using the general method with tetrabromomethane (0.60 g, 1.8 mmol) as the electrophile. Normal workup followed by preparative TLC (CH_2Cl_2–Et_2O–heptane 1:1:3) afforded 210 mg (83%) of 1-(benzyloxy)-5-bromopyrazole (**4e**) (R_f = 0.56), identical with the material above. The second fraction contained 21 mg (12%) of unchanged starting material **2a**.

1-(Benzyloxy)-5-chloropyrazole (4d). The general procedure was used with hexachloroethane (0.47 g, 2 mmol) as the electrophile. Normal workup and preparative TLC (CH_2Cl_2–Et_2O–pentane 1:1:8) afforded 164 mg (79%) of 1-(benzyloxy)-5-chloropyrazole (**4d**) as an oil (R_f = 0.59), crystallization from pentane gave mp 26 °C. An analytical sample of **4d** was obtained by ball tube distillation at 0.04 mmHg (oven temperature 50 °C): ^{1}H-NMR ($CDCl_3$) δ 7.38–7.33 (m, 5H), 7.27 (d, J = 2.4 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 5.27 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 133.0 (d), 132.8 (s), 129.8 (d), 129.2 (d), 128.4 (d), 121.0 (s), 102.6 (d), 80.7 (t). Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.76; H, 4.51; N, 13.54. The second fraction contained 28 mg (16%) starting material **2a**.

1-(Benzyloxy)-5-iodopyrazole (4f). The general procedure was used with iodine (0.38 g, 1.5 mmol) as the electrophile. Addition of $Na_2S_2O_3$, 5 H_2O (1 g) dissolved in 10 mL of H_2O resulted in a clear solution. Normal workup and flash chromatography (gradient elution: CH_2Cl_2–Et_2O–heptane 1:1:20 → 1:1:10) provided 281 mg (94%) of 1-(benzyloxy)-5-iodopyrazole (**4f**) as an oil. An analytical sample of **4f** was obtained by ball tube distillation at 0.03 mmHg (oven temperature 80 °C): R_f (CH_2Cl_2–Et_2O–heptane 1:1:6) 0.38; ^{1}H-NMR ($CDCl_3$) δ 7.48–7.36 (m, 5H), 7.34 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 5.28 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 135.7 (d), 132.9 (s), 130.0 (d), 129.3 (d), 128.5 (d), 112.6 (d), 80.9 (t), 73.4 (s). Anal. Calcd for $C_{10}H_9IN_2O$: C, 40.02; H, 3.02; N, 9.33. Found: C, 40.21; H, 3.09; N, 9.26.

1-(Benzyloxy)-5-(trimethylsilyl)pyrazole (4g). The general procedure was used with trimethylsilyl chloride (0.26 mL, 2 mmol) as the electrophile. Addition of saturated $NaHCO_3$ (5 mL), water (5 mL), and CH_2Cl_2 (10 mL), separation of the organic layer, extraction of the aqueous phase with CH_2Cl_2, drying, and removal of solvents followed by flash chromatography (gradient elution: CH_2Cl_2–Et_2O–pentane 1:1:20 → 1:1:10) provided 214 mg (87%) of 1-(benzyloxy)-5-(trimethylsilyl)pyrazole (**4g**) as an oil. An analytical sample of **4g** was obtained by ball tube distillation at 0.02 mmHg (oven temperature 80 °C): R_f (CH_2Cl_2–Et_2O–pentane 1:1:8) 0.53; ^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 5H), 7.31 (d, J = 2.2 Hz, 1H), 6.20 (d, J = 2.2 Hz, 1H), 5.35 (s, 2H), 0.24 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 134.8 (s), 133.7 (s), 132.9 (d), 129.2 (d), 128.8 (d), 128.5 (d), 110.6 (d), 79.6 (t), −1.5 (q). Anal. Calcd for $C_{13}H_{18}N_2OSi$: C, 63.37; H, 7.36; N, 11.37. Found: C, 63.57; H, 7.46; N, 11.65.

1-(Benzyloxy)-5-(tributylstannyl)pyrazole (4h). The general method was used with tributylstannyl chloride (0.40 mL, 1.5 mmol) as the electrophile. Normal workup and flash chromatography (gradient elution: CH_2Cl_2–Et_2O–heptane 1:1:20 → 1:1:8) provided 416 mg of (90%) of 1-(benzyloxy)-5-(tributylstannyl)pyrazole (**4h**) as an oil: R_f (CH_2Cl_2–Et_2O–heptane 1:1:4) 0.52; ^{1}H-NMR ($CDCl_3$) δ 7.37 (br s, 6H), 6.14 (d, J = 2.1 Hz, 1H), 5.33 (s, 2H), 1.55 - 0.98 (m, 18H), 0.85 (t, J = 7.2 Hz, 9H); ^{13}C-NMR ($CDCl_3$) δ 133.9 (s), 133.7 (s), 133.6 (d), 129.1 (d), 128.7 (d), 128.4 (d), 111.2 (d), 79.5 (t), 28.7 (t), 27.0 (t), 13.5 (t), 10.1 (q). Anal. Calcd for $C_{22}H_{36}N_2OSn$: C, 57.04; H, 7.83; N, 6.05. Found: C, 57.23; H, 7.69; N, 6.32.

1-(Benzyloxy)-5-(methylthio)pyrazole (4i). Using the general method with dimethyl disulfide (0.27 mL, 3 mmol) as the electrophile gave, after normal workup and flash chromatography (CH_2Cl_2–Et_2O–pentane 1:1:10), 210 mg (95%) of 1-(benzyloxy)-5-(methylthio)pyrazole (**4i**) as an oil. An analytical sample of **4i** was obtained by ball tube distillation at 0.06 mmHg (oven temperature 110 °C): R_f (CH_2Cl_2–Et_2O–pentane 1:1:10) 0.45; ^{1}H-NMR ($CDCl_3$) δ 7.48–7.32 (m, 5H), 7.27 (d, J = 2.3 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 5.29 (s, 2H), 2.31 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 133.2 (s), 133.0 (d), 130.0 (s), 129.7 (d), 129.0 (d), 128.3 (d), 105.4 (d), 80.3 (t), 17.2(q). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.58; H, 5.49; N, 12.72; S, 14.55. Found: C, 60.14; H, 5.67; N, 12.47; S, 14.32.

Rearrangement of 1-[(*tert*-Butyldiphenylsilyl)oxy]-pyrazole (2b) into 1-Hydroxy-5-(*tert*-butyldiphenylsilyl)-pyrazole (6a). To a solution of 1-[(*tert*-butyldiphenylsilyl)-oxy]pyrazole (**2b**) (286 mg, 0.89 mmol) and 0.15 mL of TMEDA in 6 mL of dry THF at −78 °C was added dropwise 0.67 mL (0.97 mmol) of *n*-BuLi (1.45 M in hexane). After 5 min, trimethylsilyl chloride (0.17 mL, 1.34 mmol) was added. Stirring was continued for 1 h, and the solution was allowed to warm to rt over 1 h and stirred for further 1 h. Addition of saturated NH_4Cl (5 mL), water (5 mL), and Et_2O (20 mL), separation of the organic layer, extraction of the aqueous phase with Et_2O, drying, and removal of solvents gave 284 mg (99%) of 1-hydroxy-5-(*tert*-butyldiphenylsilyl)pyrazole (**6a**), mp 156–162 °C. Low temperature recrystallization (EtOAc/heptane) gave mp 169 °C: ^{1}H-NMR ($CDCl_3$) δ 7.60–7.55 (m, 4H), 7.46–7.31 (m, 6H), 7.01 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.4 Hz, 1H), 1.20 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 135.8 (d), 133.0 (s), 131.3 (d), 130.6 (s), 129.5 (d), 127.6 (d), 113.9 (d), 28.3 (q), 18.4 (s). Anal. Calcd for $C_{19}H_{22}N_2OSi$: C, 70.77; H, 6.88; N, 8.69. Found: C, 70.64; H, 6.90; N, 8.77.

Debenzylation of 1-(Benzyloxy)pyrazoles. 1-Hydroxy-5-chloropyrazole (6b). A mixture of 1-(benzyloxy)-5-chloropyrazole (**4d**) (425 mg, 2.04 mmol) and 3 mL of aqueous hydrogen bromide (47%) was stirred for 5 h at 60 °C. The mixture was washed with CH_2Cl_2 (5 × 5 mL), and the volume of the washings was reduced to ca. 5 mL and back-extracted with 47% aqueous HBr (2 × 1 mL). To the combined HBr phases were added potassium dihydrogenphosphate (0.5 g) and water (5 mL), and the pH was adjusted to *ca.* 1 with 33% aqueous sodium hydroxide. Extraction with CH_2Cl_2–Et_2O (4:1, 10 × 10 mL), drying of the combined organic phases, and removal of solvents afforded 241 mg (100%) of 1-hydroxy-5-chloropyrazole (**6b**): mp 143.5 °C; ^{1}H-NMR ($CDCl_3$) δ 11.15 (br s, 1H), 7.17 (d, J = 2.7 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 131.4 (d), 122.5 (s), 103.0 (d). Anal. Calcd for $C_3H_3ClN_2O$: C, 30.40; H, 2.55; N, 23.64. Found: C, 30.36; H, 2.47; N, 23.44.

1-Hydroxypyrazole (1). 1-(Benzyloxy)pyrazole (**2a**) (174 mg, 1.0 mmol), 34 mg of 10% Pd on activated carbon, and MeOH (5 mL) were stirred under hydrogen (1 atm) at 0 °C for 30 min. Filtration through celite (ca. 0.1 g) and removal of the methanol produced 78 mg (93%) of 1-hydroxypyrazole (**1**), identical with the material described previously.[14]

1-Hydroxy-5-(trimethylsilyl)pyrazole (6c). Similarly, hydrogenolysis of 174 mg (0.71 mmol) of 1-(benzyloxy)-5-(trimethylsilyl)pyrazole (**4g**) for 2 h at 0 °C produced 109 mg (99%) of 1-hydroxy-5-(trimethylsilyl)pyrazole (**6c**): mp 94 °C (EtOAc–heptane); ^{1}H-NMR ($CDCl_3$) δ 12.05 (br s, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 0.33 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 135.2 (s), 131.0 (d), 109.9 (d), −1.8 (q). Anal. Calcd for $C_6H_{12}N_2OSi$: C, 46.12; H, 7.74; N, 17.93. Found: C, 46.27; H, 7.74; N, 17.75.

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