Regioselective Introduction of Electrophiles in the 4-Position of 1-Hydroxypyrazole via Bromine−Lithium Exchange

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Two protocols for introduction of electrophiles at the 4-position of 1-hydroxypyrazoles have been developed. The first is deprotonation of 4-bromo-1-[(*tert*-butyldiphenylsilyl)oxy]pyrazole (**6**) with LDA to produce the 5-lithio derivative in which the silyl group migrates spontaneously from oxygen to C-5 affording 4-bromo-5-(*tert*-butyldiphenylsilyl)-1-lithoxypyrazole (**8**). Subsequent treatment with *t*-BuLi causes bromine−lithium exchange to give 5-*tert*-butyldiphenylsilyl-4-lithio-1-lithoxypyrazole which is trapped with electrophiles affording 4-substituted 5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazoles **9a**−**e** in a one-pot sequence. The second is treatment of 4-bromo-1-hydroxypyrazole (**5**) with excess LDA and trimethylsilyl chloride to produce 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**), which upon sequential metalation with *n*-BuLi and reaction with electrophiles affords 4-substituted 3,5-bis(trimethylsilyl)-1-hydroxypyrazoles **13a**−**e**. The *tert*-butyldiphenylsilyl group of **9a** and the trimethylsilyl groups of **12** can be removed selectively by treatment with tetrabutylammonium fluoride in THF in the presence of trifluoroacetic acid.

Introduction

1-Substituted pyrazoles can be lithiated at the 5-position by treatment with organolithium reagents, and the 5-lithiopyrazoles formed react with a series of different electrophiles to give 1,5-disubstituted pyrazoles.[1,2] Subsequent N-deprotection gives access to 3(5)-substituted pyrazoles.[1,3,4] 1-Substituted pyrazoles readily undergo electrophilic halogenation[5,6] and nitration[7] at the 4-position giving access to only halo- and nitro-substituted pyrazoles. An alternative approach to 4-substituted pyrazoles would be reaction of 4-lithiopyrazoles with electrophiles. However, there are only a few examples of pyrazole C-4 lithiation,[8−13] all based on bromine−lithium exchange. This reaction sometimes proceeds with low chemoselectivity due to competing deprotonation at C-5[8,14] or isomerization of initially formed 4-lithiopyrazole to 5-lithiopyrazole.[15] Obviously, these problems can be avoided by introducing a protection group at C-5. We selected silyl protecting groups for this purpose since they could be easily introduced by metalation−silylation and removed again after the crucial metalation at C-4. This allowed for a one-pot sequence.

Results and Discussion

Attempted Metalation at C-4. We first attempted direct lithiation of the 4-position in 1-benzyloxy-5-trimethylsilylpyrazole (**1c**)[2] using *n*-BuLi. However, **1c** was lithiated at the benzylic CH_2 group, affording the anion **2** which underwent N−O bond cleavage producing 1-lithio-5-trimethylsilylpyrazole and benzaldehyde. The latter compound reacted with *n*-BuLi, and aqueous workup gave 3(5)-trimethylsilylpyrazole (**3**) and 1-phenyl-1-pentanol (Scheme 1).[16] To avoid lateral deprotonation we attempted lithiation of 1-(9-phenylfluoren-9-yloxy)-5-(trimethylsilyl)pyrazole (**1a**) or 1-hydroxy-5-(*tert*-butyldiphenylsilyl)pyrazole (**1b**)[2] which are devoid of benzylic protons. However, these compounds remained unchanged upon treatment with *n*-, *sec*-, or *t*-BuLi (Scheme 1). Obviously the 4-proton in these pyrazole derivatives is not sufficiently acidic to be abstracted by butyllithium bases. Therefore, halogen−lithium exchange was investigated. However, when 4-bromo-1-hydroxypyrazole (**5**) was treated with *t*-BuLi followed by reaction with MeOD, a 15:30:40:15 mixture of 1-hydroxypyrazole (**4**) together with its 4-bromo-5-deuterio, 4-deuterio, and 5-deuterio derivatives was obtained indicating poor chemoselectivity and thermodynamically instability of initially formed 4-lithio-1-lithoxypyrazole. These experiments show that selective lithiation at C-4 requires a 4-bromopyrazole

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(1) For a recent review on lithiated pyrazoles, see: Grimmett, M. R.; Iddon, B. *Heterocycles* **1994**, *37*, 2087.
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(7) Hüttel, R.; Büchele, F.; Jochum, P. *Chem. Ber.* **1955**, *88*, 1577.
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(12) Elguero, J.; Jaramillo, C.; Pardo, C. *Synthesis* **1997**, 563.
(13) Jeon, D. J.; Yu, D. W.; Yun, K. Y.; Ryu, E. K. *Synth. Commun.* **1998**, *28*, 2159.
(14) Treatment of 1-benzyloxy-4-bromopyrazole with *n*-BuLi at −78 °C for 5 min followed by addition of MeOD produced a 1:1:1 mixture of 1-benzyloxy-5-[^{2}H]-pyrazole, 1-benzyloxy-4-[^{2}H]-pyrazole, and 1-benzyloxy-4-bromo-5-[^{2}H]-pyrazole according to ^{1}H NMR.
(15) Tertov, B. A.; Morkovnik, A. S. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1975**, *11*, 343.
(16) Uhlmann, P.; Felding, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1997**, *62*, 9177.

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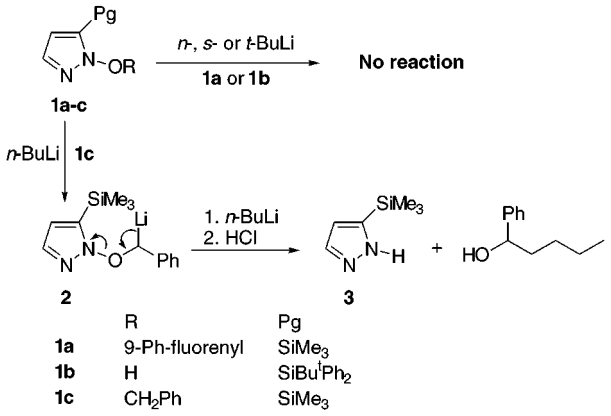
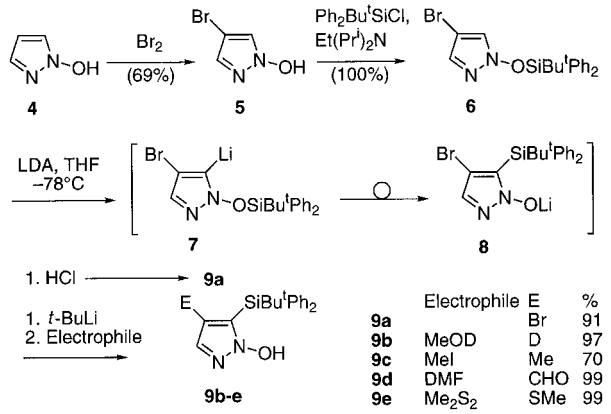
Scheme 1



Scheme 2

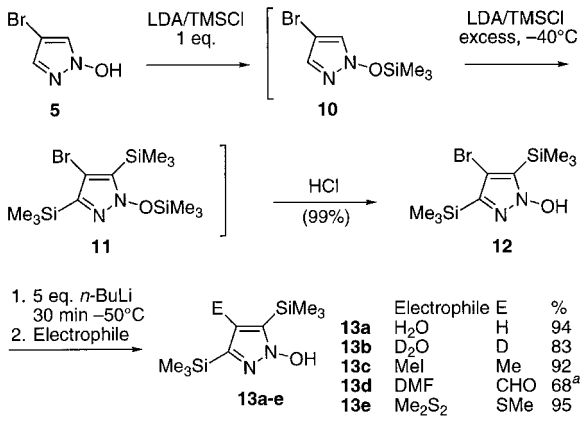


protected at the 5-position and two successful strategies were then developed as described below.

Preparation of 4-Substituted 5-(*tert*-Butyldiphenylsilyl)-1-hydroxypyrazoles. 4-Bromo-1-[(*tert*-butyldiphenylsilyl)oxy]pyrazole (**6**) was obtained by bromination of 1-hydroxypyrazole (**4**) to give 4-bromo-1-hydroxypyrazole (**5**) which was O-silylated under standard conditions producing **6** in quantitative yield. Treatment of **6** with the soft base *n*-BuLi gave rise to a complicated mixture, probably due to competing bromine−lithium exchange and deprotonation. In contrast, the hard base LDA afforded exclusively C-5 deprotonation which was followed by the previously observed[2] spontaneous migration of the *tert*-butyldiphenylsilyl group from the *N*-oxygen to C-5 affording the 4-bromo-5-silyl-protected pyrazole **9a** (91% yield) upon aqueous workup. If the aqueous workup was omitted, subsequent selective and quantitative bromine−lithium exchange of the intermediate **8** by adding excess *t*-BuLi could be accomplished in the same pot. Quenching of the putative intermediate 5-*tert*-butyldiphenylsilyl-1-lithoxypyrazol-4-yllithium with deuterio, carbon, or sulfur electrophiles produced 4-substituted 5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazoles **9b**−**e** in good to excellent yields (Scheme 2). By way of example, the *tert*-butyldiphenylsilyl protecting group of **9a** was removed by heating the solution to reflux in THF containing tetrabutylammonium fluoride (TBAF) and 1 equiv of trifluoroacetic acid (TFA) to give **5** in 91% yield (Scheme 4). The presence of TFA was essential for obtaining high yields. Fluoride ion-catalyzed protiodesilylation proceeds via an intermediate anion;[17] therefore

(17) Eaborn, C.; Seconi, G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 925.

Scheme 3



[a] 2.2 equiv *tert*-BuLi was used instead of *n*-BuLi.

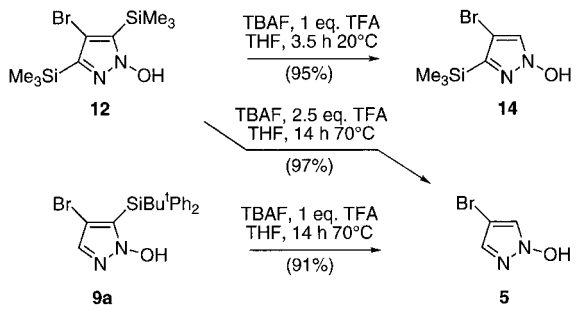
the role of the TFA may be that it protonates the *N*-oxygen so that formation of an unfavorable O,C-dianion is avoided. This hypothesis was supported by the fact that desilylation of the O-protected 1-benzyloxy-5-(*tert*-butyldiphenylsilyl)pyrazole could be achieved by TBAF in THF at 0 °C in the absence of TFA.

Preparation of 4-Substituted 3,5-Bis(trimethylsilyl)-1-hydroxypyrazoles. To find a more labile and less sterically demanding silyl protecting group, use of the trimethylsilyl group was investigated. Attempts to isolate 4-bromo-1-(trimethylsilyloxy)pyrazole (**10**) failed due to its ready desilylation. However **10** could be generated in situ by reaction of 4-bromo-1-hydroxypyrazole (**5**) with LDA in the presence of 1 equiv of trimethylsilyl chloride. Subsequent treatment with excess LDA produced 4-bromo-1-hydroxy-5-(trimethylsilyl)pyrazole together with 6−8% of 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) and 15−20% of 4-bromo-1-hydroxypyrazole (**5**). Even in the presence of only 0.9 equiv of trimethylsilyl chloride, formation of **12** could not be avoided. Neither regioselectivity between C-3 and C-5 or monoselectivity could be achieved; therefore C-3 and C-5 disilylation was attempted using an excess of LDA and trimethylsilyl chloride for in situ trapping[18,19] of the pyrazole anions. This afforded 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) in 99% yield (Scheme 3). Presumably, O-silylation of **5** is followed by deprotonation and silylation at C-5 and then deprotonation and silylation at C-3. To the best of our best knowledge, this is the first example of deprotonation at the 3-position of 1-substituted pyrazoles.[20] Most likely, the bromine at C-4 enhances the acidity of H-3 since similar treatment of 1-hydroxypyrazole (**4**) produced 1-hydroxy-5-(trimethylsilyl)pyrazole as the only product. The extended reaction time (3.5 h) and elevated temperature (−40 °C instead of −78 °C) indicate that the 3-lithiopyrazole is formed sluggishly.

As shown in Scheme 3, pyrazole **12** underwent bromine−lithium exchange when treated with 5 equiv of *n*-BuLi. Deprotonation of the *N*-hydroxy group took place prior to bromine−lithium exchange since complete regeneration of the starting material was observed when

(18) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.
(19) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.
(20) We have previously reported the 3,5-bistrimethylsilylation of 2-benzylpyrazole 1-oxide via repeated deprotonation and C-silylation.[21] Pavlik et al.[22] have reported the preparation of 3-lithio-1-methylpyrazole via bromine−lithium exchange.

Scheme 4



only 1 equiv of *n*-BuLi was used. After addition of the first equivalent of *n*-BuLi, the reaction mixture turns dark yellow indicating the start of formation of the putative dianion 4-lithio-3,5-bis(trimethylsilyl)-1-lithoxypyrazole. Performing the bromine−lithium exchange at −78 °C for 1 h resulted in only 92% exchange. However complete bromine−lithium exchange was achieved in 30 min at −50 °C. The relatively long reaction time as compared to other halogen−metal exchange reactions[23] most likely is due to the slow formation of dianions in solution and to the bulkiness of the adjacent trimethylsilyl groups. Quenching 4-lithio-3,5-bis(trimethylsilyl)-1-lithoxypyrazole with deuterio, carbon, or sulfur electrophiles produced 4-substituted 3,5-bis(trimethylsilyl)-1-hydroxypyrazoles **13a**−**e** in good to excellent yields (Scheme 3). Attempts to use more bulky electrophiles such as trimethylsilyl chloride or benzaldehyde failed. In the preparation of **13d**, better results were obtained when only 2.2 equiv of *t*-BuLi and 1.2 equiv of DMF were used. Increasing the amount of DMF gave rise to complicated mixtures. The facile removal of the silyl protecting groups was illustrated by the monoselective desilylation of 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) using TBAF in THF in the presence of equivalent amounts of TFA. The trimethylsilyl group at the 5-position[24] was readily removed at room temperature whereas removal of the trimethylsilyl group at C-3 required heating to 70 °C for 14 h (Scheme 4). The observed regioselectivity in this fluoride ion-catalyzed protiodesilylation reflects that in pyrazoles the 5-anion is more stable than the 3-anion.[26]

Conclusions

In conclusion, we have demonstrated that 4-lithio-1-lithoxypyrazoles can be generated by bromine−lithium exchange in the presence of silyl protecting groups at C-5 or at C-3 and C-5. These species can be used to obtain otherwise difficultly accessible C-4 funtionalized 1-hydroxypyrazoles. The silyl protecting groups could be removed readily as exemplified by the desilylation of **9a** and **12** by treatment with TBAF in THF and in the presence of TFA.

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. Unless otherwise indicated, the reaction mixtures were worked up by addition of saturated aqueous NH_4Cl and CH_2Cl_2, isolation of the organic layer, extraction of the aqueous phase with CH_2Cl_2, drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the filtrate in vacuo. Flash chromatography (FC) 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 or a 300 MHz instrument.[27]

Materials. All solvents and reagents were obtained from Fluka or Aldrich and used without further purification except TMEDA which was distilled from CaH_2, THF which was distilled from Na/benzophenone under nitrogen, and DMF which was sequentially dried with and stored over 3 Å molecular sieves. *n*-, *sec*-, and *tert*-Butyllithium were titrated prior to use.[28]

1-(9-Phenylfluoren-9-yloxy)-5-(trimethylsilyl)pyrazole (1a). To a solution of 1-(9-phenylfluoren-9-yloxy)pyrazole[2] (1.04 g 3.22 mmol) and TMEDA (0.63 mL, 4.2 mmol) in 20 mL of dry THF was added dropwise 1.4 M *n*-BuLi in hexanes (3.0 mL, 4.20 mmol) at −78 °C. After 20 min, trimethylsilyl chloride (0.82 mL, 6.5 mmol) was added. Stirring was continued for 1 h, and the solution was allowed to warm to room temperature over 1 h and stirred for further 1 h. Standard workup and FC (heptane → CH_2Cl_2−Et_2O−heptane 1:1:8) provided 1.25 g (98%) of 1-(9-phenylfluoren-9-yloxy)-5-(trimethylsilyl)pyrazole **(1a)**, mp 108 °C (heptane): R_f(CH_2Cl_2−Et_2O−heptane 1:1:8) 0.51; ^{1}H NMR ($CDCl_3$) δ 7.68−7.57 (m, 4 H), 7.40−7.30 (m, 5 H), 7.16 (d, J = 2.1 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 2 H), 6.92 (d, J = 7.5 Hz, 2 H), 6.04 (d, J = 2.2 Hz, 1 H), −0.26 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 144.2 (s), 141.3 (s), 140.6 (s), 137.5 (s), 132.4 (d), 129.6 (d), 128.0 (d), 127.9 (d), 127.7 (d), 126.3 (d), 126.1 (d), 119.9 (d), 110.0 (d), 97.1 (s), −1.85 (q). Anal. Calcd for $C_{25}H_{24}N_2OSi$: C, 75.72; H, 6.10; N, 7.06. Found: C, 75.95; H, 6.31; N, 6.89.

3(5)-Trimethylsilylpyrazole (3). To a solution of 1-benzyloxy-5-(trimethylsilyl)pyrazole (**1c**) (246 mg, 1 mmol) and TMEDA (0.30 mL, 2.0 mmol) in dry THF (10 mL) was added dropwise 1.6 M *n*-BuLi in hexanes (1.25 mL, 2.0 mmol)[29] at −78 °C. After 10 min, D_2O (0.30 mL) was added and stirring was continued for 5 min before the solution was allowed to warm to 0 °C. Standard workup and FC (CH_2Cl_2−Et_2O−pentane 1:1:20 → 1:1:0) provided 144 mg (88%) of 1-phenyl-1-pentanol, R_f(CH_2Cl_2−Et_2O−pentane 1:1:8) 0.33 and 119 mg (84%) of 3(5)-trimethylsilylpyrazole (**3**), mp 76 °C (pentane) (lit.[30] mp 79−80 °C): R_f(CH_2Cl_2−Et_2O 1:1) 0.45; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 1.7 Hz, 1 H), 6.44 (d, J = 1.7 Hz, 1 H), 0.32 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 142.4 (s), 138.6 (d), 112.1 (d), −1.23 (q).

4-Bromo-1-hydroxypyrazole (5). Bromine (1.55 mL, 30 mmol) was added dropwise to a mixture of 1-hydroxypyrazole (**4**)[27] (2.49 g, 29.6 mmol) and 48% aqueous HBr (1.7 mL) in 60 mL of CH_2Cl_2 at −78 °C. Stirring was continued for 1 h, and the solution was allowed to warm to room temperature over 1 h and stirred for further 12 h resulting in a brown inhomogeneous solution. Addition of $Na_2SO_3 \cdot 7H_2O$ (3 g) dissolved in

(21) Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 625.
(22) Pavlik, J. W.; Kurzweil, E. M. *J. Heterocycl. Chem.* **1992**, *29*, 1357.
(23) Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 4431.
(24) The position of the trimethylsilyl group of **14** was assigned by comparison of the ^{13}C NMR signals with those of 4-bromo-1-hydroxypyrazole (**5**). In **14** and **5** C-5 resonate at 123.1 and 121.8 ppm, respectively, while C-3 resonate at 144.7 and 131.6 ppm, respectively. The 13.1 ppm downfield shift of C-3 in **14** agrees with the shift displacement induced by a trimethylsilyl group. Furthermore, $^1J_{C-5,H-5}$ and $^3J_{C-3,H-5}$ in **14** (199.3 and 7.8 Hz) resemble those observed in **5** (199.1 and 7.7 Hz). This agrees with the values found in other 1-substituted pyrazoles.[25]
(25) Begtrup, M.; Boyer, G.; Cabildo, P.; Cativiela, C.; Claramunt, R. M.; Elguero, J.; Garcia, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.* **1993**, *31*, 107.
(26) Effenberger, F.; Krebs, A. *J. Org. Chem.* **1984**, *49*, 4687.
(27) Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 243.
(28) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.
(29) Using only 1 equiv of *n*-BuLi/TMEDA resulted in 48% starting material **1c** together with 44% of 1-phenyl-1-pentanol and 41% of **3**.
(30) Birkofer, L.; Franz, M. *Chem. Ber.* **1972**, *105*, 1759.

30 mL of H_2O gave a clear solution. Addition of Et_2O (50 mL), separation of the organic layer, extraction of the aqueous phase five times with ether, drying of the combined organic phases ($MgSO_4$), filtration, and evaporation gave 4.88 g of a mixture of 4-bromo-1-hydroxypyrazole (**5**), dibrominated 1-hydroxypyrazole, and unchanged starting material **4** in the ratio 79:13:8 (^{1}H NMR). A single recrystallization from EtOAc−heptane (1:6, ca. 35 mL) gave 3.33 g (69%) of 4-bromo-1-hydroxypyrazole (**5**), mp 133 °C: ^{1}H NMR ($(CD_3)_2CO$) δ 11.6 (br s, 1H), 7.72 (d, J = 1.1 Hz, 1H), 7.21 (d, J = 1.1 Hz, 1H); ^{13}C NMR ($(CD_3)_2CO$) δ 131.6 (dd, $^1J_{C-3,H-3}$ = 194.8, $^3J_{C-3,H-5}$ = 7.7 Hz, C-3), 121.8 (dd, $^1J_{C-5,H-5}$ = 199.1, $^3J_{C-5,H-3}$ = 2.9 Hz, C-5), 88.9 (dd, $^2J_{C-4,H-5}$ and $^2J_{C-4,H-3}$ 5.9 and 6.4 Hz, C-4). Anal. Calcd for $C_3H_3BrN_2O$: C, 22.11; H, 1.86; N, 17.19. Found: C, 22.02; H, 1,84; N, 16.93.

4-Bromo-1-[*tert*-(butyldiphenylsilyl)oxy]pyrazole (6). To a solution of 4-bromo-1-hydroxypyrazole (**5**) (2.59 g, 15.9 mmol) and *N*-ethyldiisopropylamine (2.80 mL, 16.3 mmol) in 15 mL of CH_2Cl_2 at −20 °C was added dropwise *tert*-butyldiphenylsilyl chloride (4.20 mL, 16.3 mmol). Stirring was continued at room temperature for 12 h. Removal of the CH_2Cl_2 afforded a solid that was extracted with ether (4 × 50 mL). The combined ether phases were filtered and evaporated to dryness. Extraction with 50 °C heptane (4 × 50 mL), filtration through activated carbon, and removal of the heptane gave 6.40 g (100%) of 4-bromo-1-[*tert*-(butyldiphenylsilyl)oxy]pyrazole (**6**),[31] mp 66−69 °C (EtOAc−heptane): ^{1}H NMR ($CDCl_3$) δ 7.73−7.67 (m, 4H), 7.51−7.33 (m, 6H), 6.98 (d, J = 1.05 Hz, 1H), 6.95 (d, J = 1.05 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.6 (d), 132.0 (d), 130.6 (d), 130.1 (s), 127.7 (d), 121.8 (d), 89.9 (s), 26.5 (q), 19.2 (s). Anal. Calcd for $C_{19}H_{21}BrN_2OSi$: C, 56.86; H, 5.27; N, 6.98. Found: C, 57.11; H, 5.40; N, 6.67.

Rearrangement of 4-Bromo-1-[*tert*-(butyldiphenylsilyl)oxy]pyrazole (6) into 4-Bromo-5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazole (9a). Freshly prepared LDA (2.99 mmol) in 6 mL of THF was added dropwise during 2 min to a solution of 4-bromo-1-(*tert*-butyldiphenylsilyloxy)pyrazole (**6**) (610 mg, 1.52 mmol) in THF (15 mL) at −78 °C. Stirring was continued at −78 °C for 10 min, and aquesous HCl (4 M, 10 mL) was added. The solution was allowed to warm to room temperature and extracted five times with Et_2O. Removal of the solvent in vacuo and FC (HOAc−EtOAc−heptane 1:10:100 → 1:10:50) gave 560 mg (91%) of 4-bromo-5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazole (**9a**), mp 173−175 °C: R_f (HOAc−EtOAc−heptane 1:10:100) 0.13; ^{1}H NMR ($CDCl_3$) δ 7.7−7.3 (m, 10 H), 7.07 (s, 1 H), 1.28 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 136.0, 133.9, 132.4, 130.0, 129.6, 127.7, 101.0, 28.5, 19.0. Anal. Calcd for $C_{19}H_{21}BrN_2OSi$: C, 56.86; H, 5.27; N, 6.98. Found: C, 57.02; H, 5.38; N, 7.02.

Rearrangement of 4-Bromo-1-[*tert*-(butyldiphenylsilyl)oxy]pyrazole (6) into 4-Bromo-1-lithoxy-5-(*tert*-butyldiphenylsilyl)pyrazole (8) Followed by Bromine−Lithium Exchange and Reaction with an Electrophile. General. Freshly prepared LDA (2 mmol) in 4 mL of THF was added dropwise during 2 min to a solution of 4-bromo-1-(*tert*-butyldiphenylsilyloxy)pyrazole (**6**) (401 mg, 1.00 mmol) in THF (8 mL) at −78 °C. Stirring was continued at −78 °C for 10 min, 1.44 M *t*-BuLi in pentane (2.78 mL, 4 mmol) was added over 1 min, and the mixture was stirred at −78 °C for a further 3 min before addition of the electrophile.

5-(*tert*-Butyldiphenylsilyl)-4-[^{2}H]-1-hydroxypyrazole (9b). The general method was used with monodeuteriomethanol (0.60 mL, 15 mmol) as the electrophile. After stirring at −78 °C for 30 min, the solution was allowed to warm to 0 °C over 10 min. Standard workup gave 314 mg (97%) of 5-(*tert*-butyldiphenylsilyl)-4-[^{2}H]-1-hydroxypyrazole (**9b**). The ^{1}H NMR spectrum was identical with the spectrum of 5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazole[2] except that the signal for H-4 at 6.18 ppm was absent, indicating quantitative deuteration at the 4-position.

5-(*tert*-Butyldiphenylsilyl)-1-hydroxy-4-methylpyrazole (9c). The general method was used with methyl iodide (0.73 mL, 11.7 mmol) as the electrophile. After stirring at −78 °C for 30 min, 33% dimethylamine in ethanol (6 mL) was added in order to destroy excess methyl iodide, and the solution was allowed to warm to room temperature. Addition of saturated aqueous NH_4Cl (10 mL), adjustment of pH to 2 using 2 M HCl followed by extraction five times with Et_2O, drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the filtrate in vacuo followed by FC (HOAc−EtOAc−heptane 1:10:200 → 1:10:50) gave 234 mg (70%) of 5-(*tert*-butyldiphenylsilyl)-1-hydroxy-4-methylpyrazole (**9c**), mp 202−204 °C (EtOAc−heptane 1:4): R_f(HOAc−EtOAc−heptane 1:10:100) 0.09; ^{1}H NMR ($CDCl_3$) δ 7.70−7.30 (m, 10 H), 6.91 (s, 1 H), 1.28 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 135.9, 133.7, 131.8, 129.4, 128.2, 127.8, 123.6, 28.7, 18.9, 11.2. Anal. Calcd for $C_{20}H_{24}N_2OSi$: C, 71.39; H, 7.19; N, 8.32. Found: C, 71.29; H, 7.28; N, 8.24.

5-(*tert*-Butyldiphenylsilyl)-4-formyl-1-hydroxypyrazole (9d). The general method was used with DMF (0.54 mL, 7 mmol) as the electrophile. After stirring at −78 °C for 30 min, the solution was allowed to warm to 0 °C over 1 h and stirred for a further 1 h. Addition of 2 M HCl (10 mL), stirring at room temperature for 1 h, separation of the organic phase, extraction of the aqueous phase with CH_2Cl_2, drying of the combined organic phases ($MgSO_4$), filtration, and evaporation of the filtrate in vacuo followed by FC (EtOAc−heptane 1:4 → 1:1) gave 348 mg (99%) of 5-(*tert*-butyldiphenylsilyl)-4-formyl-1-hydroxypyrazole (**9d**), mp 190−191 °C (EtOAc−heptane 1:4): R_f(EtOAc−heptane 1:1) 0.34; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 7.71 (s, 1 H), 7.60−7.34 (m, 10 H), 1.31 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 186.0, 136.0, 135.7, 134.1, 132.1, 130.3, 128.6, 128.3, 28.7, 18.9. Anal. Calcd for $C_{20}H_{22}N_2O_2Si$: C, 68.54; H, 6.33; N, 7.99. Found: C, 68.46; H, 6.35; N, 7.97.

5-(*tert*-Butyldiphenylsilyl)-1-hydroxy-4-(methylthio)-pyrazole (9e). Using the general procedure, with dimethyl disulfide (0.68 mL, 7.6 mmol) as the electrophile and workup as described for 1-hydroxy-4-methyl-5-(*tert*-butyldiphenylsilyl)-pyrazole (**9c**) gave 364 mg (99%) of 5-(*tert*-butyldiphenylsilyl)-1-hydroxy-4-(methylthio)pyrazole (**9e**), mp 133−135 °C (EtOAc−heptane 1:4): R_f(HOAc−EtOAc−heptane 1:10:100) 0.11; ^{1}H NMR ($CDCl_3$) δ 7.80−7.30 (m, 10 H), 6.97 (s, 1 H), 1.85 (s, 3 H), 1.27 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 136.0, 134.2, 133.1, 131.5, 129.4, 127.5, 121.2, 28.5, 19.5, 18.9. Anal. Calcd for $C_{20}H_{24}N_2OSSi$: C, 65.18; H, 6.56; N; 7.60 Found: C, 65.43; H, 6.72; N, 7.65.

3,5-Bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (12). A freshly prepared solution of LDA (37.4 mmol) in 30 mL of THF was added at −78 °C during 4 min to a solution of 4-bromo-1-hydroxypyrazole (**5**) (1.51 g, 9.29 mmol) and trimethylsilyl chloride (7.4 mL, 58 mmol) in 20 mL of THF. The reaction mixture was stirred at −50 to −40 °C for 3.5 h, quenched with 4 M HCl (20 mL), and allowed to warm to room temperature. The aqueous phase was extracted five times with Et_2O, and the combined organic phases were washed with brine and water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 2.82 g (99%) of 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**), mp 157−159 °C (pentane): ^{1}H NMR ($CDCl_3$) δ 0.43 (s, 9H), 0.35 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 143.7 (s), 132.2 (s), 106.2 (s), −0.8 (q), −1.1 (q). Anal. Calcd for $C_9H_{19}BrN_2OSi_2$: C, 46.84; H, 7.86; N, 10.92. Found: C, 47.07; H, 7.77; N, 10.91.

Lithiation of 3,5-Bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (12) Followed by Reaction with an Electrophile. General. To a solution of 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) (307 mg, 1.0 mmol) in THF (10 mL) was added dropwise 1.6 M *n*-BuLi in hexanes (3.13 mL, 5.0 mmol) at −78 °C over 2 min. The dark yellow solution was stirred at −78 °C for 5 min and at −50 °C for 30 min and then cooled to −78 °C whereupon the electrophile was added.

3,5-Bis(trimethylsilyl)-4-[^{2}H]-1-hydroxypyrazole (13b). The general method with D_2O (1.2 mL, 60 mmol) as the electrophile was used. After stirring at −78 °C for 5 min, the reaction mixture was allowed to warm to room temperature over 30 min. Addition of 2 M HCl (10 mL), separation of the organic layer, extraction of the aqueous layer with CH_2Cl_2, washing of the combined organic phases with water, drying

(31) **6** partially desilylated upon attempted flash chromathography.

($MgSO_4$), filtration, and evaporation in vacuo gave 190 mg (83%) of 3,5-bis(trimethylsilyl)-[^{2}H]-1-hydroxypyrazole (**13b**) as a solid. The ^{1}H and ^{13}C NMR spectra were similar to those of 3,5-bis(trimethylsilyl)-1-hydroxypyrazole (**13a**) except that the ^{1}H NMR signal at 6.29 ppm was missing, indicating that the extent of deuteration was >99%. The ^{13}C NMR signal at 116.5 ppm was a triplet ($^1J_{C-4,\ D-4} = 28$ Hz) with low intensity, characteristic for a deuterio-substituted carbon atom.

3,5-Bis(trimethylsilyl)-1-hydroxypyrazole (13a). Using the general method, with H_2O (1.08 mL, 60 mmol) as the electrophile and reaction conditions and workup as described for 3,5-bis(trimethylsilyl)-[^{2}H]-1-hydroxypyrazole (**13b**) gave 215 mg (94%) of 3,5-bis(trimethylsilyl)-1-hydroxypyrazole (**13a**), mp 146−149 °C (pentane): ^{1}H NMR ($CDCl_3$) δ 6.29 (s, 1H) 0.35 (s, 9H), 0.27 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 143.8 (s), 132.9 (s), 116.5 (d), −1.1 (q), −1.7 (q). Anal. Calcd for $C_9H_{20}N_2OSi_2$: C, 47.32; H, 8.82; N, 12.26. Found: C, 47.71; H, 8.72; N, 12.24.

3,5-Bis(trimethylsilyl)-1-hydroxy-4-methylpyrazole (13c). The general method was used with methyl iodide (0.19 mL, 3 mmol) as the electrophile. Stirring at −78 °C for 10 min and at −40 °C for 1 h, addition of aqueous 2 M HCl (10 mL), workup as described for 3,5-bis(trimethylsilyl)-[^{2}H]-1-hydroxypyrazole (**13b**), and FC (HOAc−EtOAc−heptane 1:10:300 → 1:10:100) gave 222 mg (92%) of 3,5-bis(trimethylsilyl)-1-hydroxy-4-methylpyrazole (**13c**), mp 144−147 °C (pentane): R_f(HOAc−EtOAc−heptane 1:10:100) 0.39; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 0.37 (s, 9H), 0.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 141.3 (s), 130.4 (s), 127.2 (s), 11.5 (q), −0.85 (q), −0.87 (q). Anal. Calcd for $C_{10}H_{22}N_2OSi_2$: C, 49.54; H, 9.15; N, 11.55. Found: C, 49.43; H, 9.10; N, 11.78.

3,5-Bis(trimethylsilyl)-4-formyl-1-hydroxypyrazole (13d). To a solution of 3,5-bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) (324 mg, 1.05 mmol) in THF (10 mL) at −78 °C was added *t*-BuLi (1.53 mL, 2.31 mmol) over 2 min. The reaction mixture was stirred at −78 °C for 5 min and at −50 °C for 30 min. After cooling to −78 °C, DMF (0.096 mL, 1.26 mmol) was added. The mixture was stirred at −78 °C for 1 h, quenched with 4 M HCl (10 mL), and allowed to warm to room temperature followed by workup as described for 3,5-bis(trimethylsilyl)-[^{2}H]-1-hydroxypyrazole (**13b**). FC (HOAc−EtOAc−heptane 1:10:200 → 1:10:75) gave 183 mg (68%) of 3,5-bis(trimethylsilyl)-4-formyl-1-hydroxypyrazole (**13d**), mp 183−184 °C (pentane−EtOAc 10:1): R_f(HOAc−EtOAc−heptane 1:10:100) 0.33; ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 1H), 0.48 (s, 9H), 0.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 185.3 (d), 150.9 (s), 138.5 (s), 133.0 (s), −0.70 (q), −1.33 (q). Anal. Calcd for $C_{10}H_{20}N_2O_2Si_2$: C, 46.84; H, 7.86; N, 10.92. Found: C, 47.07; H, 7.77; N, 10.91.

3,5-Bis(trimethylsilyl)-1-hydroxy-4-(methylthio)pyrazole (13e). The general method was used with dimethyl disulfide (0.90 mL, 10 mmol) as the electrophile. Stirring at −78 °C for 1 h and at room temperature for 3 h, addition of aqueous 2 M HCl (10 mL), workup as described for 3,5-bis(trimethylsilyl)-[^{2}H]-1-hydroxypyrazole (**13b**), and FC (HOAc−EtOAc−heptane 1:10:300 → 1:10:100) gave 261 mg (95%) of 3,5-bis(trimethylsilyl)-1-hydroxy-4-(methylthio)pyrazole (**13d**), mp 145−146 °C (pentane): R_f(HOAc−EtOAc−heptane 1:10:100) 0.33; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 0.47 (s, 9H), 0.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 149.7 (s), 136.8 (s), 124.1 (s), 23.6 (q), −0.43 (q), −0.56 (q). Anal. Calcd for $C_{10}H_{22}N_2OSSi_2$: C, 43.75; H, 8.08; N, 10.20. Found: C:, 44.07; H, 8.13; N, 10.14.

Desilylation of C-Silylated 4-Bromo-1-hydroxypyrazoles. 4-Bromo-1-hydroxypyrazole (5). A solution of 4-bromo-5-(*tert*-butyldiphenylsilyl)-1-hydroxypyrazole (**9a**) (250 mg, 0.62 mmol), TBAF·$3H_2O$ (980 mg, 3.1 mmol), and TFA (0.050 mL, 0.65 mmol) in THF (4 mL) was refluxed for 14 h under a nitrogen atmosphere. After cooling to room temperature and addition of 4 M HCl (3 mL), the solution was extracted five times with Et_2O. The combined organic phases were dried ($MgSO_4$), and the ether was removed in vacuo. FC (HOAc−EtOAc−heptane 1:10:200 → 1:10:25) gave 92 mg (91%) of 4-bromo-1-hydroxypyrazole (**5**), identical with the material described above.

4-Bromo-1-hydroxy-3-(trimethylsilyl)pyrazole (14). 3,5-Bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) (123 mg, 0.40 mmol), TBAF·$3H_2O$ (500 mg, 1.58 mmol), and TFA (0.030 mL, 0.40 mmol) were mixed in THF (8 mL) at 0 °C. The solution was stirred at room temperature for 3.5 h, 4 M HCl (4 mL) was added, and the reaction mixture was worked up as above. FC (HOAc−EtOAc−heptane 1:10:200 → 1:10:50) gave 89 mg (95%) of 4-bromo-1-hydroxy-3-(trimethylsilyl)-pyrazole (**14**) as a pale yellow oil:[24] R_f(HOAc−EtOAc−heptane 1:10:100) 0.10; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 144.7 (ddec, $^3J_{C-3,H-5} = 7.8$, $^3J_{C-3,SiMe3} = 2$ Hz, C-3), 123.1 (d, $^1J_{C-5,H-5} = 199.3$ Hz, C-5), 98.2 (d, $^2J_{C-4,H-5} = 5.7$ Hz, C-4), −1.64 (qhep, $^1J = 120.4$, $^3J = 2.0$ Hz). Anal. Calcd for $C_6H_{11}BrN_2OSi$: C, 30.65; H, 4.72; N, 11.91. Found: C, 30.93; H, 4.52; N, 11.64.

4-Bromo-1-hydroxypyrazole (5). 3,5-Bis(trimethylsilyl)-4-bromo-1-hydroxypyrazole (**12**) (144 mg, 0.47 mmol), TBAF·$3H_2O$ (0.60 g, 1.90 mmol), and TFA (0.096 mL, 1.28 mmol) were mixed in THF (10 mL) at 0 °C. The solution was refluxed for 14 h under an argon atmosphere. Addition of 4 M HCl (5 mL) and standard workup as above followed by FC (HOAc−EtOAc−heptane 1:10:200 → 1:10:25) gave 74 mg (97%) of 4-bromo-1-hydroxypyrazole (**5**), identical with the material described above.

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