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Metalated 1-(*p*-Methoxybenzyl)pyrazole: A Structural Chameleon

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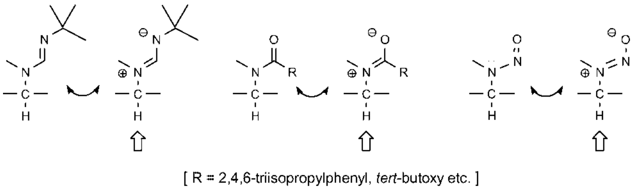
When treated with either butyllithium or lithium diisopropylamide, 1-(*p*-methoxybenzyl)pyrazole undergoes metalation at the exocyclic α-position but mutates to the 5-lithio species in the course of few minutes or hours. Trapping the intermediates with a rapidly reacting electrophile such as chlorotrimethysilane or carbon dioxide offers selective access to either of the two possible regioisomers. On the other hand, the relatively inert 1-iodobutane and butyl trifluoromethanesulfonate ("triflate") inevitably give rise to product mixtures, as the 5-lithio species is more slowly intercepted than it can revert to the α-metallomer by a rapid, though intermolecular, dynamic equilibration process.

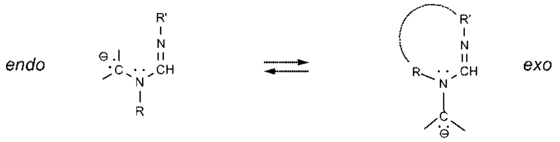
Introduction

Among all acidifying effects, the so-called *dipole stabilization* is a particularly intriguing phenomenon. It has been invoked to rationalize the ease with which saturated positions adjacent to the trivalent (saturated) nitrogen atom in amidines, carboxamides, or carbamates and *N*-nitrosoamines can be deprotonated.[1a] At first sight one may feel inclined to attribute the increased *CH*-acidity to the partially zwitterionic character of the substrates (Scheme 1). This would imply an ylide-like electron distribution in the deprotonated species. However, a closer inspection which is corroborated by quantum chemical calculations[2,3] rather suggests an orthogonally σ-coupled π-polarization[4–9] to be responsible for the observed attenuation of electron excess.



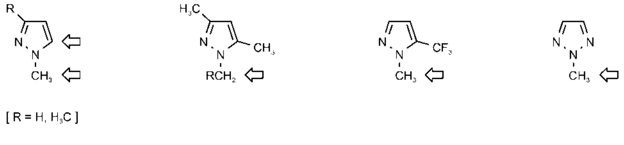
Scheme 1. Amidines, carboxamides, and *N*-nitrosoamines as precursors to dipole-stabilized organometallic species.

To incorporate the amidine unit into a small ring eliminates all uncertainty about whether the deprotonated carbon is located at the *endo* or the *exo* side of the diazaenolate backbone (Scheme 2). In this respect, imidazole may be conceived as a cyclic amidine and pyrazole as a vinylogous analog thereof.



Scheme 2. Amidines bearing a carbanion substituent at either the *endo* or the *exo* position of the saturated nitrogen atom.

Due to the high proton mobility at the 2-position[1b] and, to a lesser extent, 5-position of imidazoles, only few examples[10,11] of *exo*cyclic metalations in this heterocyclic series are known so far. In contrast, a handful of pyrazoles were reported to be deprotonated by organometallic bases at least partially at an *N*-alkyl substituent. Thus, 1-methylpyrazole[12] and 1,3-dimethylpyrazole[13] were found to be attacked by butyllithium at the *N*-methyl group and the 5-position in the ratios 1:12 and 1:2, respectively. 1,3,5-Trimethylpyrazole and even 1-ethyl-3,5-dimethylpyrazole afforded solely the corresponding 2-pyrazolylacetic and 2-pyrazolylpropionic acids when treated consecutively with butyllithium or *tert*-butyllithium and dry ice.[12] 1-Methyl-5-(trifluoromethyl)pyrazole[14] and 2-methyl-1,2,3-triazole,[15] when allowed to react with butyllithium, also underwent exclusive metalation at the *N*-methyl group (as evidenced by the purity of the trapping products isolated in 85% and 17% yield) (Scheme 3).[14]



Scheme 3. Deprotonation of *N*-methyl (or *N*-alkyl) groups attached to pyrazole or 1,2,3-triazole rings.

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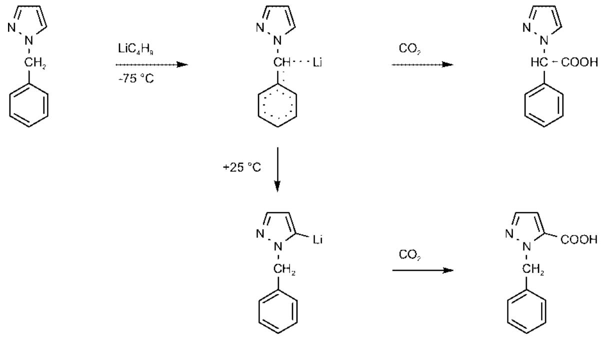
As a resonance-providing phenyl group must significantly enhance the proton mobility at the neighboring position, 1-benzylpyrazole should undergo metalation preferentially at the exocyclic methylene group. Surprisingly, however, the 1-benzylpyrazole-5-carboxylic acid (57%) was reported to be the only product after metalation with phenyllithium in diethyl ether at ambient temperature followed by carboxylation.[16] A reexamination solved the puzzle.[12] Initial metalation, accomplished with butyllithium in tetrahydrofuran at –75 °C, occurred indeed at the benzylic position. Quenching the reaction mixture with dry ice gave 2-phenyl-1-pyrazylacetic acid (32%) exclusively (Scheme 4). However, when brought to +25 °C, the organometallic intermediate isomerized by transmetalation, the lithium moving from the α- to the 5-position. As a consequence, the ensuing carboxylation afforded 1-benzylpyrazole-5-carboxylic acid (19%) (Scheme 4).[12]



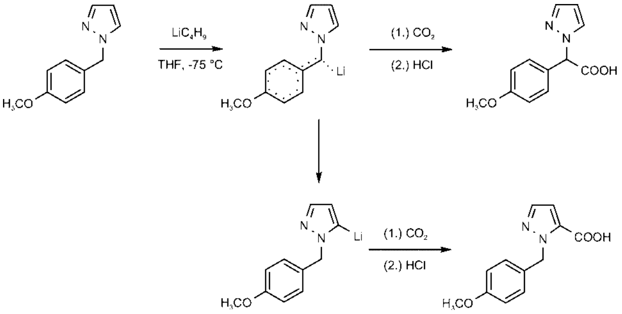
Scheme 4. Metallomeric isomerization of α-lithiated to 5-lithiated 1-benzylpyrazole.

This metallotropic isomerization is fascinating even if one cannot consider it as unequivocally established as long as the product yields remain as poor as they are. Therefore, we decided to start an in-depth investigation into the kinetics and energetics of such processes and, at the same time, to replace 1-benzylpyrazole by 1-(*p*-methoxybenzyl)pyrazole as the model compound. Being known to retard the metalation of benzylic positions,[17] the *p*-methoxy substituent may help to better control the α-lithio/5-lithio competition. Moreover, there are practical reasons that argue for such a substrate change. The *p*-methoxybenzyl ("PMB") entity is a protective group which can be easily removed not only by hydrogenolysis[18,19] (as benzyl itself), but also by oxidation[19,20] or by cleavage under acidic conditions.[21,22]

Results and Discussion

According to a preliminary study,[22] 1-(*p*-methoxybenzyl)pyrazole does react with butyllithium in tetrahydrofuran to afford 5-substituted derivatives upon trapping with various electrophiles in 30–80% yield. When 1-iodobutane was employed, trace amounts of a byproduct were obtained, which may have originated from a contaminating intermediate carrying the metal at the benzylic α-position.

Our first objective was to determine the regioisomeric composition of the product mixture as a function of the metalation time. To this end, 1-(*p*-methoxybenzyl)pyrazole was treated consecutively with butyllithium in tetrahydrofuran at –75 °C and, after fixed intervals, with dry ice and hydrochloric acid. Each time, an aliquot was converted into the methyl esters by using an excess of ethereal diazomethane. As revealed by calibrated gas chromatographic analysis, the two isomeric products 2-(4-anisyl)-2-(1-pyrazolyl)acetic acid (**1**) and 1-(*p*-methoxybenzyl)pyrazole-5-carboxylic acid (**2**) were present in the ratios 92:8, 3:97, and 1:99 and in the combined yields 67, 84, and 86% after 5, 45, and 120 min of exposure to butyllithium. Extrapolating back to zero time led to the **1**/**2** ratio 97:3. Thus, the first metalation took place almost exclusively at the benzylic α-position before the intermediate metamorphosed to the virtually pure 5-lithio species (Scheme 5).



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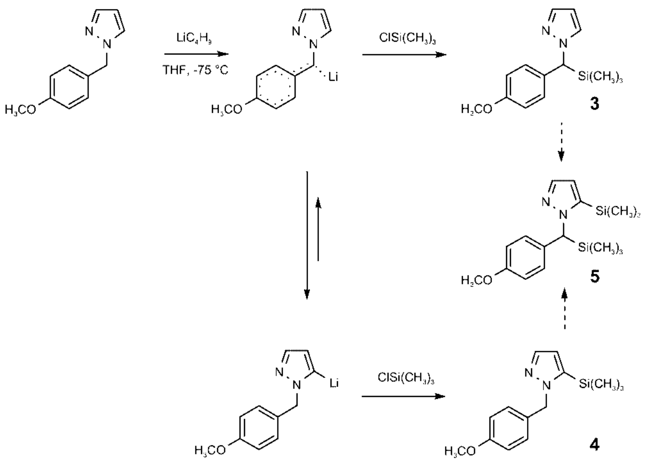
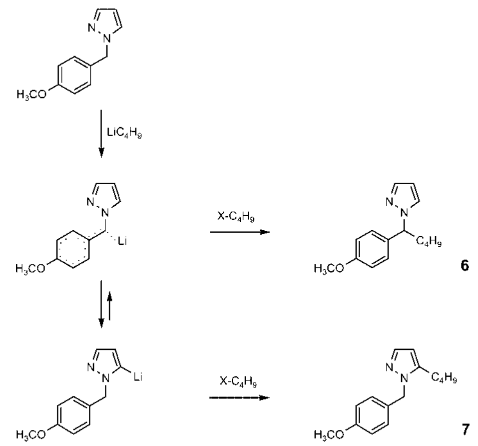
Scheme 5. Metallomeric isomerization of α-lithiated to 5-lithiated 1-benzylpyrazole.

When after 2 h of incubation with butyllithium the transient organometallic intermediate was trapped with chlorotrimethylsilane, again the 5-substituted derivative, 1-(*p*-methoxybenzyl)-5-(trimethylsilyl)pyrazole (**4**) was formed predominantly. The crude reaction mixture contained the α-substituted isomer **3** and 1-(*p*-methoxybenzyl)-5-(trimethylsilyl)pyrazole (**4**) in a 1:40 ratio along with traces (approx. 2%) of unconsumed starting material (combined yield 96%). However, when the deprotonation was accomplished with lithium diisopropylamide (LIDA), a 9:1 mixture (95%) of the silane **4** and a new product, α,5-bis(trimethylsilyl)pyrazole **5**, resulted (Scheme 6). Finally, when the LIDA-generated organolithium species was intercepted under in situ trapping conditions (chlorotrimethylsilane and LIDA being simultaneously present), 1-[*p*-methoxy-α-(trimethylsilyl)benzyl]pyrazole (**3**, 60%) was isolated as the sole product (Scheme 6).

Noteworthy conclusions can be drawn from these findings. As demonstrated by the in situ trapping experiment, the α-lithio intermediate reacts faster with chlorotrimethylsilane than it isomerizes to the 5-lithio species. On the other hand, the interception of the latter by chlorotrimethylsilane must be a relatively slow process as the back-isomerization to the α-metallomer can compete with it when diisopropylamine (the LIDA-derived byproduct) is present. On the other hand, no back-isomerization was observed within the



Scheme 6. 5-Trimethylsilylation of 1-(*p*-methoxybenzyl)pyrazoles under equilibrating conditions, but α-trimethylsilylation by in situ trapping.



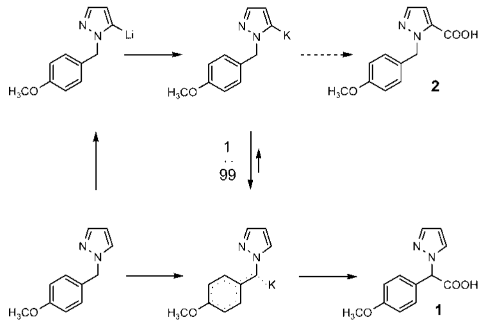
[X = I, F_3CSO_2O]

Scheme 7. Balancing the time scales of metallomeric equilibration and electrophilic trapping: exclusive α-attack of 1-iodobutane and α/5 random reaction of butyl triflate.

2-h interval when the organometallic intermediate was generated with butyllithium. The role played by the amine component suggests an *inter*molecular isomerization mechanism which involves proton abstraction from unconsumed 1-(*p*-methoxybenzyl)pyrazole by a metalated derivative thereof (specifically, LIDA) and rules out an *intra*molecular countercurrent change of places by hydrogen and lithium. This hypothesis is further confirmed by a very strong solvent effect on the rate of metallomeric isomerization. When 1-(*p*-methoxybenzyl)pyrazole was treated with butyllithium in *toluene* at –75 °C for 45 min before the mixture was quenched with dry ice, the 2-(4-anisyl)-2-(1-pyrazolyl)acetic acid (**1**, 59%) formed was contaminated by not more than trace amounts of the isomeric 1-(*p*-methoxybenzyl)-pyrazole-5-carboxylic acid (**2**, 1.2%). The rates of transmetalation processes are known to depend critically on the polarity of the medium.[23,24]

The existence of a fairly rapid, dynamic equilibrium between the α- and the 5-metallomer is further supported by experiments in which the trapping reagent is varied. When 1-(*p*-methoxybenzyl)pyrazole was lithiated with butyllithium and kept at –75 °C for 45 min before being treated with 1-iodobutane, the sole product identified was 1-[1-(*p*-anisyl)pentyl]pyrazole (**6**, 96%). In contrast, a 1:6 mixture (43%) of compound **6** and 5-butyl-1-(*p*-methoxybenzyl)pyrazole (**7**) was obtained along with unconsumed starting material (56%), when the lithiation was performed with LIDA and butyl trifluoromethanesulfonate was employed as the electrophile (Scheme 7). Alkylating reagents are known to favor delocalized (electronically “soft”), as opposed to tightly bound, organometallic centers. This intrinsic preference makes 1-iodobutane condense selectively with the α-metallomer even if present only in low equilibrium concentrations, whereas the triflate mainly attacks the 5-position, as it reacts much faster than the rate at which metallomeric isomerization restores the α-lithio species consumed (Scheme 7).

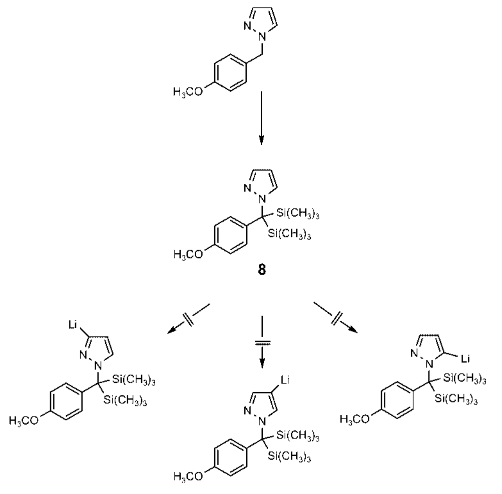
A unique feature of our model system is the ease with which the metallomeric isomerization occurs. This implies a relatively low barrier of activation in both directions and, as a corollary, an energetic compatibility of both equilibrating species. Even if the 5-lithio metallomer is indisputably less basic than the α-lithio isomer, the difference in thermodynamic stability may amount to just 1.5 or 2.0 kcal·mol^{-1}. Small changes in the experimental parameters may suffice to invert this situation. In fact, when the metalation of 1-(*p*-methoxybenzyl)pyrazole is accomplished with the superbasic mixture[1c,24] (LIC-KOR) of butyllithium and potassium *tert*-butoxide rather than with butyllithium alone, the α-metal species, presumably a potassium-containing derivative, persists. When trapped with dry ice after 2 h of reaction time, it affords a 99:1 mixture (mass balance 95%) of 2-(4-anisyl)-2-(1-pyrazolyl)acetic acid (**1**, 74%) and the 5-pyrazolecarboxylic acid (**2**, <1%). This α/5 ratio represents an equilibrium composition that is also attained when potassium *tert*-butoxide is added at –75 °C to a solution of 5-lithiated 1-(*p*-methoxybenzyl)pyrazole in tetrahydrofuran. Obviously, the resonance stabilization of the benzylic center increases[1d] when the C–Li bond is replaced by the more polar C–K bond (Scheme 8).



Scheme 8. Metal effects on metallomeric stabilities, lithium favoring the 5-metalated, potassium the α-metalated species.

The results reported above provide guidance for synthetically oriented work involving organometallic pyrazole derivatives. At the same time they offer new insight into factors that govern organometallic stability and reactivity.

A final feature in this respect concerns the relative kinetic acidity of the various pyrazole ring positions. In addition to the ring strain, which activates more or less evenly all three vacant positions, the coordinative power of the trivalent amine nitrogen, as opposed to the imine nitrogen, appears to constitute the dominant factor. Metalation at the 3- or 4-position seems impossible unless the 5-position is occupied by a strongly electron-withdrawing substituent such as a trifluoromethyl group.[14,25] 1-[*p*-Methoxy-α,α-bis(trimethylsilyl)benzyl]pyrazole (**8**), which was readily prepared in 97% yield by simultaneous treatment of 1-(*p*-methoxybenzyl)pyrazole with two equivalents of each chlorotrimethylsilane and LIDA, has a sterically inaccessible 5-position. It proved to be totally inert toward both LIDA and lithium tetramethylpiperidide (LITMP) even in the presence of *N*,*N*,*N′*,*N′′*,*N′′*-pentamethyldiethylenetriamine and potassium *tert*-butoxide (Scheme 9).



Scheme 9. Inertness of 1-[*p*-methoxy-α,α-bis(trimethylsilyl)benzyl]pyrazole toward metalating reagents.

Experimental Section

Generalities: Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[26–28] ^{1}H- and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. All samples were dissolved in deuterochloroform. Mass spectra were obtained at an ionization potential of 70 eV while a source temperature of 200 °C was maintained.

1. Pyrazolylcarboxylic Acids

1-(4-Methoxybenzyl)-1*H*-pyrazol-1-ylacetic Acid (1): Potassium *tert*-butoxide (2.8 g, 25 mmol) and 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) were consecutively added to a solution of butyllithium (25 mmol) in hexanes (17 mL) and tetrahydrofuran (0.10 L) kept in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (3 × 25 mL), and acidified with hydrochloric acid (2.0 м, 30 mL) to pH 1. The precipitate was collected by filtration, washed with water (2 × 25 mL), and dried. Recrystallization from a mixture of ethyl acetate and heptanes gave colorless prisms; m.p. 143–145 °C (decomp.); yield: 3.75 g (65%). ^{1}H NMR: δ = 9.56 (s, broad, 1 H), 7.68 (d, J = 2.0 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.35 (symm. m, 2 H), 6.93 (symm. m, 2 H), 6.34 (t, J = 2.3 Hz, 1 H), 6.22 (s, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR: δ = 171.0, 160.3, 139.2, 130.2 (3 C), 125.6, 114.6 (2 C), 105.9, 66.8, 55.3 ppm. MS: m/z (%) = 234 (7) [M$^+$ + 2], 233 (55) [M$^+$ + 1], 232 (11) [M$^+$], 189 (21), 188 (56), 187 (100), 165 (43), 121 (32). $C_{12}H_{12}N_2O_3$ (232.24): calcd. C 62.06, H 5.21; found C 62.09, H 5.11.

After acidification, a small percentage of the crude reaction mixture was treated with an ethereal solution of diazomethane until the yellow color persisted. A known amount of tetradecane, which had been calibrated before, was added as an internal standard in order to quantify the product composition by gas chromatography (2 m, 1% DB-FFAP, 200 °C, isothermal; 2 m, 2% SE-30, 200 °C). In this way, 73% methyl ester of acid **1**, 1% methyl ester of acid **2**, and 21% unconsumed starting material were identified. A very similar result (66% and 1% esters derived from acids **1** and **2**, and 23% starting material) was obtained when the substrate was first treated with butyllithium for 2 h at –75 °C before potassium *tert*-butoxide was added, and the mixture was kept for another 2 h at –75 °C.

1-(4-Methoxybenzyl)-1*H*-pyrazole-5-carboxylic Acid (2): At –75 °C, butyllithium (25 mmol) in hexanes (17 mL) was added to the solution of 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) in tetrahydrofuran (60 mL) and diethyl ether (40 mL) over a period of 1 h. The reaction mixture was kept in a dry ice/methanol bath for further 90 min before being poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (3 × 25 mL), and acidified with hydrochloric acid (2.0 м, 14 mL) to pH 1. The precipitate was collected by filtration, washed with water (2 × 25 mL), and dried to give colorless platelets (from ethyl acetate/hexanes); m.p. 161–162 °C; yield: 3.70 g (64%). ^{1}H NMR: δ = 7.59 (d, J = 2.0 Hz, 1 H), 7.24 (symm. m, 2 H), 7.00 (d, J = 2.0 Hz, 1 H), 6.83 (symm. m, 2 H), 5.73 (s, 2 H), 3.76 (s, 3 H) ppm. ^{13}C NMR: δ = 163.6, 159.3, 138.5, 131.5, 129.2 (2C), 128.9, 114.0 (2 C), 113.1, 55.2, 54.4 ppm. MS: m/z (%) = 233 (24) [M$^+$ + 1], 232 (15) [M$^+$], 188 (13), 187 (17), 121(100). $C_{12}H_{12}N_2O_3$ (232.24): calcd. C 62.06, H 5.21; found C 62.03, H 5.01. The yield was increased to 91% when butyllithium was replaced by lithium diisopropylamide as the base.

A series of further experiments was performed to assess the effect of metalation time and solvent. Neat 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (**1**, 1.9 g, 10 mmol) was added at once to a solution of butyllithium (10 mmol) in tetrahydrofuran (40 mL) and hexanes (6.3 mL), which contained in addition a known amount of tetradecane as an internal standard. Samples, withdrawn after 5, 45, and 120 min, were poured onto an excess of dry ice. When dried, the residue was acidified with hydrochloric acid (2.0 м) to pH 1 and treated with ethereal diazomethane until persistence of the yellow color. The amounts of the methyl esters of acids **1** and **2** and unconsumed starting material were determined by gas chromatography (conditions as specified above) by comparing their peak areas with that of the internal standard: 62%, 1%, and 27% (after 5 min of metalation time); 3%, 81%, and 9% (after 45 min); 1%, 5%, and 12% (after 120 min). The numbers were 59%, 1.2%, and

39% if the reaction with butyllithium was performed in toluene (at –75 °C for 45 min) rather than in tetrahydrofuran.

2. Silylated Pyrazoles

1-(4-Methoxybenzyl)-5-trimethylsilyl-1*H*-pyrazole (4): Diisopropylamine (3.7 mL, 2.7 g, 25 mmol) and 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (0.11 L) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was treated with chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) for 30 min at –75 °C. After evaporation of the volatiles, the residue was taken up in diethyl ether (80 mL) and washed with water (2×25 mL) and brine (25 mL). According to gas chromatography (30 m, DB-1701, 200 °C; 2 m, 1% DB-FFAP, 165 °C, internal standard: *m*-terphenyl), the crude product contained 3% unconsumed starting material, 86% 5-(trimethylsilyl)pyrazole **4**, and 9% presumptive α,5-bis(trimethylsilyl)pyrazole **5** (see below). The raw product was adsorbed on silica gel and eluted with a 7:3 (v/v) mixture of hexanes and ethyl acetate. The major component **4** was collected in the second fraction and, after evaporation of the solvent, isolated as a yellowish oil; b.p. 111–112 °C/0.2 Torr; m.p. –72 to –68 °C; yield: 4.32 g (66%). ^{1}H NMR: δ = 7.56 (d, J = 1.9 Hz, 1 H), 6.92 (symm. m, 2 H), 6.82 (symm. m, 2 H), 6.42 (d, J = 1.9 Hz, 1 H), 5.37 (s, 2 H), 3.76 (s, 3 H), 0.22 (s, 9 H) ppm. ^{13}C NMR: δ = 159.0, 142.5, 138.9 (2 C), 130.1, 127.7, 114.9, 114.0 (2C), 55.3, 55.1, –0.8 (3 C) ppm. MS: *m*/*z* (%) = 262 (5) [M$^+$ + 2], 261 (19) [M$^+$ + 1], 260 (20) [M$^+$], 246 (12), 245 (12), 187 (20), 121 (100). $C_{14}H_{20}N_2OSi$ (260.41): calcd. C 64.57, H 7.74; found C 64.58, H 7.70.

1-[α-(4-Methoxyphenyl)-α-(trimethylsilyl)methyl]-5-(trimethylsilyl)-1*H*-pyrazole (5): According to gas chromatography (conditions: see above), the first fraction collected by column chromatography (as described in the preceding paragraph), contained a minor component in 85% purity. It was isolated as a yellow oil; 0.59 g (7%). Its analytical data are consistent with structure **5**. ^{1}H NMR: δ = 7.53 (d, J = 1.9 Hz, 1 H), 6.93 (symm. m, 2 H), 6.78 (symm. m, 2 H), 6.36 (d, J = 1.9 Hz, 1 H), 4.85 (s, 1 H), 3.76 (s, 3 H), 0.12 (s, 9 H), 0.08 (s, 9 H) ppm. MS (MALDI-TOF): *m*/*z* (%) = 333 [M$^+$ + 1], 332 [M$^+$].

1-[(4-Methoxyphenyl)(trimethylsilyl)methyl]-1*H*-pyrazole (3): Diisopropylamine (3.7 mL, 2.7 g, 25 mmol), chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol), and 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (18 mL) and tetrahydrofuran (0.10 L) cooled in a methanol/dry ice bath. After 45 min at –75 °C, the reaction products were adsorbed on silica gel and eluted with a 7:3 (v/v) mixture of hexanes and ethyl acetate; a colorless oil was obtained; b.p. 93–95 °C/0.3 Torr; m.p. –68 to –65 °C; yield: 3.91 g (60%). ^{1}H NMR: δ = 7.50 (d, J = 1.9 Hz, 1 H), 7.32 (d, J = 2.2 Hz, 1 H), 6.99 (symm. m, 2 H), 6.80 (symm. m, 2 H), 6.24 (t, J = 2.1 Hz, 1 H), 4.83 (s, 1 H), 3.77 (s, 3 H), 0.12 (s, 9 H) ppm. ^{13}C NMR: δ = 158.1, 138.1, 132.9, 130.0, 127.3 (2 C), 113.7 (2 C), 105.4, 59.7, 55.1, –2.1 ppm. MS: *m*/*z* (%) = 261 (15) [M$^+$ + 1], 260 (60) [M$^+$], 245 (48), 218 (4), 187 (22), 165 (14), 153 (24), 121 (100). $C_{14}H_{20}N_2OSi$ (260.41): calcd. C 64.57, H 7.74; found C 64.41, H 7.63.

(Trimethylsilyl)pyrazole **4** was formed almost exclusively when 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (1.9 g, 10 mmol) was treated with butyllithium (10 mmol) in hexanes (6.6 mL) and tetrahydrofuran (40 mL) at –75 °C for 2 h before chlorotrimethylsilane (1.3 mL, 1.0 g, 10 mmol) was added. After evaporation of the volatiles, the residue was taken up in diethyl ether (30 mL) and washed with water (2×10 mL) and brine (10 mL). According to gas chromatography, the crude product contained 2.4% unconsumed starting material, 5.1% α-(trimethylsilyl)pyrazole **3**, and 91% 5-(trimethylsilyl)pyrazole **4**.

1-[(4-Methoxyphenyl)bis(trimethylsilyl)methyl]-1*H*-pyrazole (8): Diisopropylamine (26 mL, 19 g, 0.18 mol), chlorotrimethylsilane (23 mL, 20 g, 0.18 mol), and 1-(4-methoxybenzyl)-1*H*-pyrazole (17 g, 90 mmol) were added consecutively to a solution of butyllithium (0.18 mol) in hexanes (0.13 L) and tetrahydrofuran (0.32 L) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the volatiles were stripped off. The residue was extracted with pentanes (3×50 mL), and the organic solution was filtered through a pad of basic alumina. The solid left behind upon evaporation of the solvent was crystallized from pentanes as colorless platelets; m.p. 103–105 °C; yield: 29.1 g (97%). ^{1}H NMR: δ = 7.42 (d, J = 1.6 Hz, 1 H), 7.27 (d, J = 2.2 Hz, 1 H), 6.9 (m, 2 H), 6.8 (m, 2 H), 6.26 (t, J = 2.2 Hz, 1 H), 3.79 (s, 3 H), 0.09 (s, 18 H) ppm. ^{13}C NMR: δ = 156.9, 136.0, 135.1, 129.5, 128.2 (2 C), 113.0 (2 C), 105.1, 58.9, 55.0 (d, J = 3 Hz), 0.01 (6 C). MS: *m*/*z* (%) = 333 [M$^+$ + 1]. $C_{17}H_{28}N_2OSi_2$ (332.59): calcd. C 61.39, H 8.49; found C 61.45, H 8.48.

3. Butyl-Substituted Pyrazoles

1-[1-(4-Methoxyphenyl)pentyl]-1*H*-pyrazole (6): Diisopropylamine (3.7 mL, 2.7 g, 25 mmol) and 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (17 mL) and tetrahydrofuran (0.10 L) cooled in a dry ice/methanol bath. After 2 h at –75 °C, 1-iodobutane (3.3 mL, 5.0 g, 28 mmol) was added, and the reaction mixture was kept 15 h at –75 °C before the solvents were removed under reduced pressure. The residue was taken up in diethyl ether (80 mL) and washed with water (2×25 mL) and brine (25 mL). According to gas chromatography (2 m, 1% DB-FFAP, 240 °C; 2 m, 2% SE-30, 240 °C; internal standard: tetradecane), the crude product contained 72% α-butylpyrazole **6** and some 10% of a by-product, presumably α,α-dibutylpyrazole. The reaction mixture was adsorbed on silica gel and eluted with a 7:3 (v/v) mixture of hexanes and ethyl acetate. The major component **6** was collected in the second fraction and, after evaporation of the solvents, isolated as a colorless oil; b.p. 120–122 °C/0.2 Torr; m.p. –65 to –62 °C; yield: 5.14 g (84%). ^{1}H NMR: δ = 7.53 (d, J = 1.9 Hz, 1 H), 7.39 (d, J = 2.2 Hz, 1 H), 7.22 (symm. m, 2 H), 6.84 (symm. m, 2 H), 6.22 (t, J = 2.1 Hz, 1 H), 5.22 (t, J = 7.8 Hz, 1 H), 3.77 (s, 3 H), 2.4 (m, 1 H), 2.1 (m, 1 H), 1.3 (m, 2 H), 1.2 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 159.1, 138.9, 133.1, 128.1 (2 C), 127.9, 114.0 (2 C), 105.2, 65.6, 55.1, 35.2, 28.7, 22.4, 13.9 ppm. MS: *m*/*z* (%) = 245 (1) [M$^+$ + 1], 244 (1) [M$^+$], 188 (54), 187 (100), 176 (14), 147 (28), 121 (27). $C_{15}H_{20}N_2O$ (244.33): calcd. C 73.74, H 8.25; found C 73.74, H 8.25.

Butylpyrazole **6** was obtained as the sole product when a solution of 1-(4-methoxybenzyl)-1*H*-pyrazole[22] (4.7 g, 25 mmol) and butyllithium in tetrahydrofuran (0.10 L) was kept in a dry ice/methanol bath for 45 min before 1-iodobutane (2.9 mL, 4.6 g, 25 mmol) was added at once. After 6 h at –75 °C, the volatiles were stripped off. The residue was taken up in diethyl ether (80 mL), washed with water (2×25 mL) and brine (25 mL). According to gas chromatographic analysis (see above), the crude product contained 2% unconsumed starting material and 96% compound **6**.

5-Butyl-1-(4-methoxybenzyl)-1*H*-pyrazole (7): At –100 °C, butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (0.10 L) was treated consecutively with diisopropylamine (3.7 mL, 2.7 g, 25 mmol) and 1-(4-methoxybenzyl)-1*H*-pyrazole (4.7 g, 25 mmol). Butyl trifluoromethanesulfonate (25 mmol), prepared from 1-butanol (2.3 mL, 1. 9 g, 25 mmol), butyllithium (25 mmol), and trifluoromethanesulfonic anhydride (4.2 mL, 7.1 g, 25 mmol) in tetrahydrofuran (25 mL), was added. After 45 min at –75 °C, the volatiles were stripped off. The residue was taken up in diethyl ether (75 mL), washed with water (2×25 mL) and brine (25 mL). According to gas chromatography (2 m, 1% DB-FFAP, 240 °C; 2 m, 2% SE-30, 240 °C; tetradecane as the internal standard), the crude product contained 55% unconsumed starting material, 6% α-butylpyrazole **6**, and 38% 5-butylpyrazole. The raw material was adsorbed on silica gel and eluted with a 7:3 (v/v) mixture of hexanes and ethyl acetate. According to gas chromatography analysis, the first fraction contained 83% 5-butyl isomer **7**,[22] 11% α-isomer **6**, and 6% unconsumed starting material. After evaporation of the solvents, a yellowish oil was collected (0.51 g), which became reddish within a few minutes. ^{1}H NMR (signals belonging to impurities omitted): δ = 7.44 (d, J = 1.9 Hz, 1 H), 7.03 (symm. m, 2 H), 6.83 (symm. m, 2 H), 6.05 (d, J = 1.9 Hz, 1 H), 5.22 (s, 2 H), 3.77 (s, 3 H), 2.52 (t, J = 7.7 Hz, 2 H), 1.54 (quint, J = 7.7 Hz, 2 H), 1.34 (symm. m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 159.1, 143.0, 138.5, 129.5, 128.1 (2 C), 114.1 (2 C), 104.5, 55.2, 52.5, 30.6, 25.3, 22.4, 13.8 ppm. MS: m/z (%) = 244 (7) [M$^+$], 187 (8), 121 (100), 91 (6), 78 (14).

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[1] M. Schlosser in *Organometallics in Synthesis; A Manual* (Ed.: M. Schlosser), second edition, Wiley, Chichester, **2000**, pp. 1–352; a) spec. pp. 188–192 and 251; b) spec. p. 239; c) spec. pp. 248–250; d) spec. pp. 50–52.

[2] N. G. Rondan, K. N. Houk, P. Beak, W. J. Zajdel, J. Chandrasekhar, P. V. R. Schleyer, *J. Org. Chem.* **1981**, *46*, 4108–4110.

[3] R. D. Bach, M. L. Braden, G. J. Wolber, *J. Org. Chem.* **1983**, *48*, 1509–1514.

[4] A. Mordini, M. Schlosser, *Chimia* **1986**, *40*, 309–310.

[5] M. Schlosser, R. Lehmann, T. Jenny, *J. Organomet. Chem.* **1990**, *389*, 149–157.

[6] M. Schlosser, J. H. Choi, S. Takagishi, *Tetrahedron* **1990**, *46*, 5633–5648.

[7] Z.-p. Liu, M. Schlosser, *Heteroat. Chem.* **1991**, *2*, 515–519; *Chem. Abstr.* **1992**, *116*, 83693y.

[8] M. Schlosser, E. Castagnetti, *Chem. Eur. J.* **2002**, *8*, 799–804.

[9] I. Hyla-Kryspin, S. Grimme, H. H. Büker, N. M. M. Nibbering, F. Cottet, M. Schlosser, *Chem. Eur. J.* **2005**, *11*, 1251–1256.

[10] M. R. Cuberes, M. Moreno-Mañas, A. Trius, *Synthesis* **1985**, 302–304.

[11] M. Moreno-Mañas, J. Bassa, N. Lladó, R. Pleixats, *J. Heterocycl. Chem.* **1990**, *27*, 673–678.

[12] A. R. Katritzky, C. Jayaram, S. N. Vassilatos, *Tetrahedron* **1983**, *39*, 2023–2029.

[13] D. E. Butler, S. M. Alexander, *J. Org. Chem.* **1972**, *37*, 215–220.

[14] M. Schlosser, J.-N. Volle, F. Leroux, K. Schenk, *Eur. J. Org. Chem.* **2002**, 2913–2920.

[15] M. Schlosser, J.-N. Volle, unpublished results (**2001**).

[16] R. Hüttel, M. E. Schön, *Justus Liebigs Ann. Chem.* **1959**, *625*, 55–65.

[17] M. Schlosser, P. Maccaroni, E. Marzi, *Tetrahedron* **1998**, *54*, 2763–2770.

[18] J. Lin, C. M. Thompson, *J. Heterocycl. Chem.* **1994**, *31*, 1701–1705.

[19] I. A. Zavialov, V. H. Dahanukar, H. Nguyen, C. Orr, D. R. Andrews, *Org. Lett.* **2004**, *6*, 2237–2240.

[20] S. B. Singh, *Tetrahedron Lett.* **1995**, *36*, 2009–2012.

[21] F. Nohara, M. Nishii, K. Ogawa, K. Isono, M. Ubukata, T. Fujii, T. Itaya, T. Saito, *Tetrahedron Lett.* **1987**, *28*, 1287–1290.

[22] C. Subramanyam, *Synth. Commun.* **1995**, *25*, 761–774.

[23] H. Gilman, T. S. Soddy, *J. Org. Chem.* **1957**, *22*, 1715–1716.

[24] M. Schlosser, *J. Organomet. Chem.* **1967**, *8*, 9–16.

[25] S. Iwata, C.-P. Qian, K. Tanaka, *Chem. Lett.* **1992**, 357–360.

[26] M. Schlosser, M. Marull, *Eur. J. Org. Chem.* **2003**, 1569–1575.

[27] E. Masson, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 4401–4405.

[28] C. Heiss, F. Leroux, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 5242–5247.

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