Synthesis of 4-Substituted 1-(Benzyloxy)pyrazoles via Iodine−Magnesium Exchange of 1-(Benzyloxy)-4-iodopyrazole

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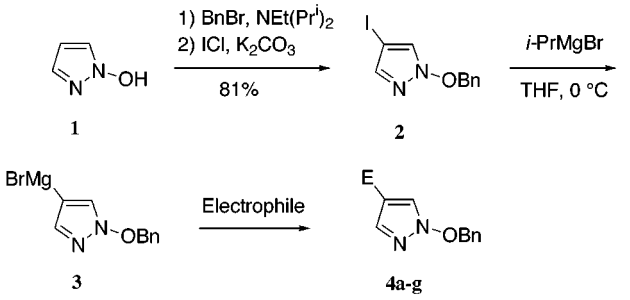
Introduction

Pyrazole anions are readily generated via direct metalation at C-5.[1] Halogen−metal exchange is an attractive route to enter ring positions of heteroaromatic systems not accessible by direct metalation. Thus, 4-lithiopyrazoles have been prepared by halogen−lithium exchange of 4-halopyrazoles,[2,3] but in some cases the reaction proceeds with low chemoselectivity due to competing deprotonation at C-5[4,5] or isomerization of the 4-lithiopyrazole to the corresponding 5-lithiopyrazole.[6] These problems have been solved by introducing protection groups at C-5.[7] Recently, iodine−magnesium exchange with ethyl- or isopropylmagnesium bromide has been described as a mild and efficient method for the generation of positionally stable aryl[8] and heteroaryl magnesium halides.[9−14] We have used this approach and report herein a protocol for the preparation of 4-substituted 1-(benzyloxy)pyrazoles without protection groups at C-5. Regiospecific monoiodination of 1-(benzyloxy)pyrazole followed by iodine−magnesium exchange and reaction with electrophiles produced the corresponding 4-substituted 1-(benzyloxy)pyrazoles. The method was extended to the synthesis of 4-aryl- and 4-heteroaryl-substituted 1-benzyloxypyrazoles by combining iodine−magnesium exchange, transmetalation with zinc chloride, and palladium-catalyzed cross-coupling.

Table 1. Introduction of Electrophiles



Entry	Electrophile	E	Product	Yield[a] (%)
1	DMF	CHO	**4a**	88
2	PhCHO	PhCH(OH)	**4b**	87[b]
3	PhCOCl	PhCO	**4c**	68
4	TsCN	CN	**4d**	81
5	TMSCl	TMS	**4e**	86
6	Ph_2PCl	Ph_2PO	**4f**	72[c]
7	Bu_3SnCl	Bu_3Sn	**4g**	99[d]

[a] Isolated yields of chromatographically pure products. [b] The crude product was reduced with $NaBH_4$. [c] The crude product was oxidised with oxygen. [d] Determined by ^{1}H-NMR of the crude product.

Results and Discussion

Introduction of Electrophiles. 1-(Benzyloxy)-4-iodopyrazole (**2**)[15] was prepared in 81% overall yield by benzylation of 1-hydroxypyrazole (**1**) followed by iodination of the crude 1-(benzyloxy)pyrazole using 3 equiv of iodine monochloride. Treatment of **2** with 1.2 equiv of *i*-PrMgBr in THF at 0 °C for 1 h[17] produced positionally stable 1-(benzyloxy)pyrazol-4-ylmagnesium bromide (**3**) in virtually quantitative yield.[18,19] 1-(Benzyloxy)pyrazol-4-ylmagnesium bromide (**3**) reacted with several electrophiles affording 4-substituted 1-(benzyloxy)pyrazoles in good yields (Table 1). When benzaldehyde was used as electrophile, a mixture of 1-(benzyloxy)-4-(phenylhydroxymethyl)pyrazole (**4b**) (33%) and 4-benzoyl-1-(benzyloxy)pyrazole (**4c**) (59%), along with benzyl alcohol, was isolated. Repeating the experiment and including treatment of the crude reaction mixture with $NaBH_4$ produced **4b** as the only product in 87% isolated yield (Table 1, entry 2). Most likely, **4c** is formed via hydride transfer from the initially generated magnesium alcoholate of **4b**

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(1) Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1995**, *60*, 4995.
(2) Elguero, J.; Jaramillo, C.; Pardo, C. *Synthesis* **1997**, 563.
(3) Hahn, M.; Heinisch, G.; Holzer, W.; Schartz, H. *J. Heterocycl. Chem.* **1991**, *28*, 1189.
(4) Hüttel, R.; Schön, M. E. *Liebigs Ann. Chem.* **1959**, *625*, 55.
(5) 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.
(6) Tertov, B. A.; Morkovnik, A. S. *Chem. Heterocycl. Comp. Eng. Transl.* **1975**, *11*, 343.
(7) Balle, T.; Vedsø, P.; Begtrup, M., in press.
(8) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701 and references therein.
(9) El Borai, M.; Hassanein, M. *Org. Prep. Proced. Int.* **1982**, *14*, 409.
(10) Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* **1997**, *53*, 14481.
(11) Kondo, Y.; Yoshida, A.; Sato, S.; Sakamoto, T. *Heterocycles* **1996**, *42*, 105.
(12) Jetter, M. C.; Reitz, A. B. *Synthesis* **1998**, 829.
(13) Turner, R. M.; Lindell, S. D. *J. Org. Chem.* **1991**, *56*, 5739.
(14) Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359.
(15) The position of the iodine of **2** was assigned by comparison of the ^{13}C NMR signals with those of 1-(benzyloxy)pyrazole.[1] In **2** and 1-(benzyloxy)pyrazole, C-4 resonates at 53.0 and 102.9 ppm, respectively, C-3 resonates at 138.6 and 133.2 ppm, and C-5 resonates at 126.8 and 122.4 ppm, respectively. The 49.9 ppm upfield shift of C-4 in **2** agrees with the shift displacement induced by iodine. Furthermore, $^1J_{C-5,H-5}$, $^1J_{C-3,H-3}$, $^3J_{C-5,H-3}$, and $^3J_{C-3,H-5}$ in **2** (199.2, 195.8, 3.2, and 8.2 Hz) resemble those observed in 1-(benzyloxy)pyrazole (192.7, 188.6, 3.8, and 9.1 Hz) and agree with the values found in other 1-substituted pyrazoles.[16] See also ref 18.
(16) 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.
(17) Attempts to generate **3** via oxidative addition of magnesium to **2** in THF failed.
(18) Quenching with D_2O gave 1-(benzyloxy)-4-[^{2}H]-pyrazole with >98% deuterium incorporation according to ^{1}H NMR.
(19) Attempts to perform the iodine−lithium exchange with *n*-BuLi or *t*-BuLi (−78 °C in THF) under conditions of reverse addition gave poor isolated yields (20−25%).

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to benzaldehyde, as previously reported for other systems.[20] Accordingly, **4b** gave **4c** and benzyl alcohol upon sequential treatment with 0.9 equiv of *i*-PrMgBr and benzaldehyde.[21] When Ph_2PCl was used as the electrophile, the initially formed trivalent phosphorus product was partially oxidized to the corresponding phosphine oxide **4f** upon workup. 1-(Benzyloxy)-4-(diphenylphosphinoyl)pyrazole (**4f**) could be obtained as the only product in 72% yield if the crude product was treated with oxygen (Table 1, entry 6).

Introduction of Aryl and Heteroaryl Substituents. To extend the scope of this methodology, the preparation of 4-aryl and 4-heteroaryl-1-(benzyloxy)-pyrazoles via transmetalation and palladium-catalyzed cross-coupling was investigated. A comparison between the Corriu−Kumada[22,23] (using **3**), Stille[24] (using **4g**), and Negishi[25] (using **5**) cross-couplings[26] revealed the latter to be the method of choice. 1-(Benzyloxy)pyrazol-4-ylmagnesium bromide (**3**) failed to react with 4-iodotoluene and 4-iodoaniline under Pd(0) catalysis.[27] Similar treatment of 1-(benzyloxy)-4-tributylstannylpyrazole (**4g**) resulted in partial destannylation producing 1-(benzyloxy)pyrazole, whereas 1-(benzyloxy)-pyrazole-4-ylzinc chloride[28] (**5**) produced the desired products in 92% and 62% yield (Table 2, entries 1 and 3), respectively. Therefore, **5** was coupled with a range of aryl iodides possessing either electron-donating or -withdrawing groups, affording the cross-coupled products **6a**−**g** in 62−92% yield (Table 2, entries 1−7). Furthermore, cross-coupling of **5** with π-excessive **2** or 2-iodothiophene or with π-deficient 2-bromopyridine produced the 4-heteroaryl-substituted 1-(benzyloxy)pyrazoles **6h**−**j** in 57−89% yield (Table 2, entries 8−10).

In conclusion, we have developed a method that permits regiospecific introduction of electrophiles in the 4-position of 1-(benzyloxy)pyrazole via iodine−magnesium exchange of 1-(benzyloxy)-4-iodopyrazole. The methodology was extended to include the introduction of aryl- and heteroarylsubstituents by combining iodine−magnesium exchange, transmetalation with $ZnCl_2$ and palladium-catalyzed Negishi cross-coupling.

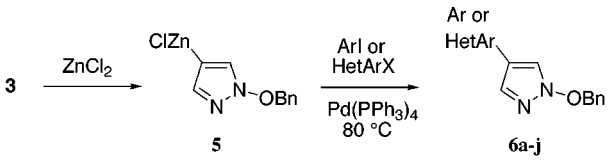
Experimental Section

General Methods. All reactions involving air-sensitive reagents were performed under N_2 using syringe−septum cap techniques. All glassware was flame-dried prior to use. Flash column chromatography (FC) was performed using silica gel (Merck, 40−63 mesh). TLC was performed using Merck silica gel 60 F_{254} aluminum sheets. The sheets were visualized under UV light (254 nm) and by spraying with ammonium cerium molybdate.[29] Melting points are uncorrected. All new compounds were colorless, unless otherwise stated. NMR spectra were recorded in $CDCl_3$ on a 300 MHz Varian spectrometer with tetramethylsilane/$CDCl_3$ as internal standards. The multiplicity of ^{13}C NMR signals were assigned from APT spectra.

Materials. All solvents and reagents were obtained from Fluka or Aldrich and used without further purification except THF, which was distilled from Na/benzophenone under nitrogen, and DMF, which was sequentially dried with and stored over 3 Å molecular sieves.[30] A 1.0 M solution of $ZnCl_2$ in THF was prepared by flame-drying $ZnCl_2$ in vacuo and dissolving it in dry THF. A 1.3 M solution of isopropylmagnesium bromide (*i*-PrMgBr) in THF was prepared as previously described[31] and titrated prior to use.[32] $Pd(PPh_3)_4$ was prepared as previously described.[33]

Preparation of 1-(Benzyloxy)-4-iodopyrazole (2). 1-Hydroxypyrazole (**1**)[34] (2.74 g, 32.6 mmol) and *N*-ethyldiisopropylamine (4.23 g, 32.7 mmol) were dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. Benzyl bromide (5.63 g, 32.8 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. NaOH (1 M, 50 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with NaOH (1 M) and water, dried over $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in $CHCl_3$ (100 mL), K_2CO_3 (13.5 g, 97.8 mmol) was added, and the reaction mixture was treated with iodine monochloride (15.9 g, 97.8 mmol) dissolved in $CHCl_3$ (15 mL). After 12 h of stirring at room temperature, the reaction was quenched with Na_2SO_3 (1 M, 75 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The organic phase was dried over $MgSO_4$ and evaporated. Two sequential low temperature (−78 °C) recrystallizations from EtOAc/heptane (1:

Table 2. Introduction of Aryl and Heteroaryl Groups



Entry	Sub	Product	Yield[a] (%)
1	Sub = 4-CH_3	**6a**	92
2	2-NH_2	**6b**	75
3	4-NH_2	**6c**	62
4	2-OMe	**6d**	83
5	4-OMe	**6e**	65
6	2-NO_2	**6f**	69
7	4-NO_2	**6g**	78
8	**2**	**6h**	89
9		**6i**	57
10		**6j**	67

[a]Isolated yields of chromatographically pure products.

(20) Marshall, J. *J. Chem. Soc.* **1915**, *107*, 509.
(21) ^1H NMR of the crude product showed a 3:1 mixture of 4-benzoyl-1-(benzyloxy)pyrazole (**4c**) and 1-(benzyloxy)-4-(phenylhydroxymethyl)pyrazole (**4b**), as well as benzyl alcohol.
(22) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.
(23) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.
(24) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
(25) Negishi, E. I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
(26) For a review on cross-coupling reactions, see: Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
(27) The reaction mixture was quenched with MeOD in both experiments. The crude products were analyzed by ^1H NMR and showed 91% deuterium incorporation in the 4-position of 1-(benzyloxy)-pyrazole when 4-iodotoluene was used, whereas 1-(benzyloxy)pyrazole was the only observed product with 4-iodoaniline, indicating high basicity of **3**.
(28) Prepared by transmetalation of 1-(benzyloxy)pyrazol-4-ylmagnesium bromide (**3**) with $ZnCl_2$; see the Experimental Section for details. Attempts to generate **5** via direct insertion of zinc (as described by Bhanu Prasad, A. S.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237) failed.
(29) Ammonium cerium molybdate: $Ce(SO_4)_2 \cdot 4H_2O$ (0.4 g) and $(NH_4)_6Mo_7O_{24}$ (20 g) dissolved in 10% H_2SO_4 (400 mL).
(30) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.
(31) Drake, N. L.; Cooke, G. B. *Org. Synth. Coll. Vol II* **1943**, 406.
(32) Lin, H.-S.; Paquette, L. *Synth. Commun.* **1994**, *24*, 2503.
(33) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
(34) Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 243.

20, 20 mL and 7 mL) gave 7.92 g (81%) of 1-(benzyloxy)-4-iodopyrazole (**2**), mp 40−41 °C (EtOAc/heptane). R_f (EtOAc/heptane, 1:4) 0.44. δ_H ($CDCl_3$): 7.40−7.28 (m, 5H), 7.32 (d, J = 0.9 Hz, 1H), 7.04 (d, J = 0.9 Hz, 1H), 5.27 (s, 2H). δ_C ($CDCl_3$): 138.6 (dd, $^1J_{C-3,H-3}$ = 195.8, $^3J_{C-3,H-5}$ = 8.2 Hz, C-3), 133.3 (s), 129.6 (d), 129.4 (d), 128.7 (d), 126.8 (dd, $^1J_{C-5,H-5}$ = 199.2, $^3J_{C-5,H-3}$ = 3.2 Hz, C-5), 80.8 (t), 53.0 (dd, $^2J_{C-4,H-5}$ and $^2J_{C-4,H-3}$ 7.9 and 6.7 Hz, C-4). Anal. Calcd for $C_{10}H_9IN_2O$: C, 40.02; H, 3.02; N, 9.33. Found: C, 40.14; H, 2.84; N, 9.24.

Iodine−Magnesium Exchange of 2 Followed by Reaction with an Electrophile. General Procedure. To a stirred solution of 1-(benzyloxy)-4-iodopyrazole (**2**) (300 mg, 1.0 mmol) in dry THF (1 mL) at 0 °C was added 1.3 M *i*-PrMgBr in THF (0.92 mL, 1.2 mmol) over 2 min. Stirring was continued for 1 h at 0 °C before the electrophile (1.5 equiv) was added. After 1 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (5 mL). Water (5 mL) was added to dissolve the formed precipitate before extraction with CH_2Cl_2 (3 × 10 mL) and drying of the combined organic phases ($MgSO_4$). Filtration and concentration in vacuo gave the crude products, which were purified by flash column chromatography, using EtOAc/heptane as eluent.

Palladium-Catalyzed Cross-Coupling of 5 with Aryl Halides. General Procedure. To a stirred solution of 1-(benzyloxy)-4-iodopyrazole (**2**) (300 mg, 1.0 mmol) in THF (1 mL) at 0 °C was added 1.3 M *i*-PrMgBr in THF (0.92 mL, 1.2 mmol) over 2 min. Stirring was continued for 1 h at 0 °C before 1 M $ZnCl_2$ in THF (1.5 mL, 1.5 mmol) was added. After 1 h of stirring at room temperature, the aryl halide (1.5 mmol) and $Pd(PPh_3)_4$ (0.02 mmol) in DMF (2.5 mL) were added. The mixture was heated to 80 °C (oil bath) for 1 h and quenched with saturated aqueous NH_4Cl (5 mL). Water (5 mL) was added to dissolve the formed precipitate before extracting with Et_2O (3 × 15 mL). Drying of the combined organic phases ($MgSO_4$), filtration, and concentration in vacuo gave the crude products which were purified by flash coloumn chromatography using EtOAc/heptane as the eluent.

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Supporting Information Available: Full experimental details for the synthesis and characterization of compound **4a**−**g** and **6a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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