Magnesium of N-Heterocycles Using *i*-PrMgCl.LiCl and Catalytic Diisopropylamine

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Supplementary Material

General

a) Purification of reagents and solvents

- THF was distilled from sodium/benzophenone
- Hexane and ethyl acetate were distilled without addition of reagents

b) Spectroscopic and Physical data

- Melting points were obtained using a Reichert hot-stage microscope, and are uncorrected
- ^1H and ^{13}C NMR spectra were recorded at 300.139 MHz and 75.035 MHz, respectively, on Bruker Avance-300 spectrometer. Spectra were recorded in deuteriated chloroform (CDCl_3) unless otherwise specified. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard at zero ppm. The ^1H NMR chemical shifts are reported: value (number of hydrogens, description of signal, coupling constant(s) in hertz (Hz) where applicable, assignment) and the ^{13}C NMR chemical shifts are reported: value (assignment). Abbreviations used: s = singlet, d = doublet, t = triplet and m = multiplet.
- Infrared spectra were obtained on Bruker Tensor 27 spectrometer. Samples were placed on a diamond tip. The absorptions are reported on the wavenumber (cm^{-1}) scale, in the range 400–4000 cm^{-1} .
- High-resolution, low-resolution and fast atom bombardment (FAB) mass spectra were recorded on a VG70-SEQ instrument. Data are quoted: m/z value (relative abundance). Samples ran on FAB were dissolved in a 3-nba matrix.

Isopropylmagnesium chloride- lithium chloride (*i*-PrMgCl.LiCl) 1

The base was prepared using the method of Knochel.¹⁻² Mg (2.673 g, 110 mmol) and anhydrous LiCl (4.25 g, 100 mmol) were dried under high vacuum at 90 °C for 30 minutes. Isopropyl chloride (9.14 ml, 100 mmol) dissolved in dry THF (50 mL) was added slowly into the flask along with few crystals of I_2 and the mixture stirred under Ar at room temperature. The reaction which starts within a few minutes was kept at room temperature and left stirring for 16 hours. The concentration was determined as follows: In a flame dried, one-neck round bottomed flask, menthol (0.312 g, 2 mmol) and 1,10-phenanthroline (4 mg) were dissolved in dry THF and stirred for 2 minutes under Ar. The Grignard solution was added drop-wise via syringe until a distinct violet colour persisted for longer than a minute. The concentration was found to be 1.33 M.

General method of Magnesiumation

To an *N*-heterocycle was added a solution of *i*-PrMgCl.LiCl (1.33 M, 1.8 eq. with respect to *N*-heterocycle, in THF) and (*i*-Pr) $_2$ NH (0.1 with respect to *N*-heterocycle). The mixture was stirred at room temperature under an argon atmosphere for 18 hours. An electrophile was added and the mixture was stirred at room temperature for 20 minutes. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL), and a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (20 mL) in the case of I_2 as an electrophile. The mixture was extracted three times with EtOAc, the organic layer was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure.

2-Iodo- *N*-Phenylsulfonylpyrrole 3

N-Phenylsulfonylpyrrole **2** (1.00 g, 4.82 mmol) was treated according to the general method, with *i*-PrMgCl.LiCl (8.78 mmol, 6.5 mL, 1.8 eq.) and (*i*-Pr)₂NH (56 μ L, 0.4 mmol, 10 mol %). After standing at room temperature for 18 hours, the reaction was treated with I₂ (3.00 g, 12.0 mmol) followed by aqueous work-up and recrystallized from 96% EtOH to give 2-iodo-*N*-phenylsulfonylpyrrole **3** (1.315 g, 70%) as brown crystals; mp. 96-98°C (Lit.³ 97-98°C); δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.91-7.94 (2H, m, Ar-H), 7.61-7.66 (1H, m, Ar-H), 7.59 (1H, dd, *J* 3.4 and 1.8, pyrrole-H), 7.50-7.56 (2H, m, Ar-H), 6.52 (1H, dd, *J* 3.4 and 1.8, pyrrole-H), and 6.27 (1H, apparent t, *J* 3.4, pyrrole-H); δ_{C} (75 MHz; CDCl₃) 147.5, 138.2, 134.2, 129.2, 128.1, 127.9, 126.7 and 114.6; HREI *m/z* 333 (M⁺, 85), 207 (7), 192 (9), 141 (46) and 77 (100) (Found: 332.9392. C₁₀H₈NO₂SI requires 332.9321).

N-Phenylsulfonylpyrrole-2-carbaldehyde 4

N-Phenylsulfonylpyrrole (2.42 mmol, 0.50 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.28 mL, 1.8 eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%). DMF (6 mmol, 0.31 mL) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give *N*-phenylsulfonylpyrrole-2-carbaldehyde (0.344 g, 60%) as an off-white solid; mp 77-78 °C (Lit.⁴ mp. 78-79 °C); δ_{H} (300 MHz; CDCl₃; Me₄Si) 9.96 (1H, s, CHO), 7.94-7.91 (2H, m, Ar-H), 7.67-7.46 (4H, m, pyrrole-H and Ar-C), 7.18 (1H, dd, *J* 3.4 and 1.7, pyrrole-H) and 6.43 (1H, apparent t, *J* 3.4, pyrrole-H); δ_{C} (75 MHz; CDCl₃) 179.2 (CHO), 138.6, 134.9, 133.9, 129.8, 127.8, 125.2 and 112.9; HREI *m/z* 235.03 (M⁺, 100).

N-[Phenyl(1*H*-Pyrrol-2yl)methylene]benzenesulfonamide 5

N-Phenylsulfonylpyrrole (2.42 mmol, 0.50 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.28 mL, 1.8 eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%). Benzonitrile (3.025 mmol, 0.33 mL) was added and the solution stirred 2 hours. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give the title compound (0.846 g, 60%); mp 145-148°C; ν_{max} (NaCl / cm⁻¹) 3428 (m, N-H), 3055 (m), 1544 (s) and 1156 (s); δ_{H} (300 MHz; CDCl₃; Me₄Si) 10.16 (1H, broad s, -NH), 7.99-7.82 (2H, m, pyrrole-H), 7.70-7.38 (8H, m, Ar-H), 7.25 (2H, m, Ar-H), 6.51 (1H, m, pyrrole-H), 6.33 (1H, m, pyrrole-H); δ_{C} (75 MHz; CDCl₃) 141.8, 132, 130.7, 129.6, 129.3, 128.6, 128.0, 127.7 and 112.3; HREI *m/z* 310.1003 (M⁺, 46), 249.1169 (10), 169.0698 (100) and 77.03945 (38) (Found 310.01003, C₁₇H₁₄N₂O₂S requires 310.0776).

2-Iodo-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide 7

N,N-Dimethylimidazole-1-sulfonamide (2.42 mmol, 0.420 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.27 mL, 1.8eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%) and left stirring at room temperature for 18 hrs. I₂ (6.0 mmol, 1.50 g) was added and the solution stirred for 10 min. The aqueous work-up gave a dark brown oil which was purified with column chromatography on silica gel using 20% EtOAc: Hexane as eluent to give 2-iodo-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide (0.568 g, 78%) as brown oil. δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.45 (1H, d, *J* 1.8, imidazole-H), 7.05 (1H, d, *J* 1.8, imidazole-H), 2.98 (6H, s, -Me); δ_{C} (75 MHz; CDCl₃) 131.2, 123.5, 83.2 and 37.8; LREI *m/z* 301.9 (M + H, 5), 300.9 (M⁺, 100), 193.9 (29) (Found 300.9376: C₅H₈N₃SO₂I requires 300.9382).

2-Formyl-*N,N*-dimethylpyrrole-1-sulfonamide 9

N,N-Dimethyl-1*H*-pyrrole-1-sulfonamide (2.42 mmol, 0.417 g) was treated according to the general method B, with *i*-PrMgCl.LiCl (4.356 mmol, 3.28 ml, 1.8eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%) and left stirring at room temperature for 18 hrs. DMF (6 mmol, 0.31 ml) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 40% EtOAc in hexane as eluent to give 2-formyl-*N,N*-dimethylpyrrole-1-sulfonamide (0.235 g, 31%) as a brown oil. V_{max} (NaCl / cm⁻¹) 1665 (CHO), 1421 (C=O), 1379, 1249 and 1153 (-SO₂-); δ_H (300 MHz; CDCl₃; Me₄Si) 10.06 (1H, s, CHO), 7.40 (1H, apparent t, *J* 1.7, pyrrole-H), 7.27-7.23 (1H, m, pyrrole-H), 6.39 (1H, apparent t, *J* 3.3, pyrrole-H) and 2.87 (6H, s, -Me); δ_C (75 MHz; CDCl₃) 179.9 (CHO), 133.9, 129.9, 122.5, 111.4 and 38.2; *m/z* HREI 202.0408 (M⁺, 100) (Found 202.0408: C₇H₁₀O₃N₂S requires 202.0412).

N,N-Dimethyl-*N'*-[phenyl(1*H*-pyrrol-2-yl)methylene]sulfamide 10

N,N-Dimethyl-1*H*-pyrrole-1-sulfonamide (2.9 mmol, 0.501 g) was treated according to the general method, with *i*-PrMgCl.LiCl (5.22 mmol, 3.92 ml, 1.8 eq) and (*i*-Pr)₂NH (0.29 mmol, 36 μ L, 10 mol%). Benzonitrile (3.025 mmol, 0.33 ml) was added and the solution stirred for 2 hours. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give the title compound (0.361 g, 25%) as a brown solid; mp. 106-108°C; δ_H (300 MHz; CDCl₃; Me₄Si) 7.60-7.41 (5H, m, Ar-H), 7.20 (1H, m, pyrrole-H), 6.50 (1H, m, pyrrole-H), 6.31 (1H, m, pyrrole-H) and 2.90 (6H, s, -Me); δ_C (75 MHz; CDCl₃) 130.8, 129.1, 128.6, 128.3, 127.4, 111.7 and 38.9; HREI *m/z* 278.18047 (M+ H, 8), 277.177 (M⁺, 40), 169.121 (100) and 77.053 (21) (Found 277.17715: C₁₃H₁₅N₃O₂S requires 277.0885).

2-Iodo-5-methoxy-1-phenylsulfonyl-1*H*-indole 12

5-Methoxy-1-phenylsulfonyl-1*H*-indole (2.42 mmol, 0.695 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.27 ml, 1.8eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%) and left stirring at room temperature for 18 hrs. I₂ (6 mmol, 1.5 g) was added and the solution stirred for 10 min. The aqueous work-up gave a dark brown oil which was purified with column chromatography on silica gel using 10% EtOAc in hexane as eluent to give 2-iodo-5-methoxy-1-phenylsulfonyl-1*H*-indole (0.849 g, 85%) as a brown solid; mp. 122- 124°C; δ_H (300 MHz; CDCl₃; Me₄Si) 8.18 (1H, d, *J* 8.2, Ar- H), 7.87 (2H, d, *J* 7.9, Ar- H), 7.55-7.53 (1H, m, indole-H), 7.46-7.41 (2H, m, Ar-H), 6.93-6.85 (3H, m, indole-H) and 3.83 (3H, s, -OMe); δ_C (75 MHz; CDCl₃) 156.9, 138.5, 134.4, 133.7, 133.1, 129.5, 127.5, 124.8, 116.8, 114.2, 102.4 and 56.0; LREI *m/z* 414.8 (M + H, 12), 412.8 (M⁺, 79), 271.8 (100) and 228.8 (10) (Found 412.9585: C₁₅H₁₂NO₃SI requires 412.9582).

1-Benzyl-2-iodo-1*H*-benzo[d]imidazole 14

N-Benzylbenzimidazole (2.42 mmol, 0.503 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.92 ml, 1.8eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%). I₂ (6 mmol, 1.50 g) was added and the solution stirred for 10 min. The aqueous workup gave a brown solid which was purified with column chromatography on silica gel using 20% EtOAc: hexane as eluent to give 1-benzyl-2-iodo-1*H*-benzo[d]imidazole (0.686 g, 85%) as a white solid; mp 118-119°C (Lit.⁵ 118-120°C); δ_H (300 MHz; CDCl₃; Me₄Si) 7.75 (1H, t, *J* 3.0, benzimidazole-H), 7.32-7.13 (8H, m, benzimidazole-H and Ar-H), 5.38 (2H, s, -CH₂-); LREI *m/z* 334.8 (M + H, 15), 333.8 (M⁺, 100), 207 (25).

1-benzyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde 15

N-Benzylbenzimidazole (2.42 mmol, 0.503 g) was treated according to method B with *i*-PrMgCl.LiCl (4.356 mmol, 3.27 ml, 1.8 eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%). DMF (6 mmol, 0.31 ml) was added and the solution stirred for 30 min. The aqueous work-up gave a brown oil which was purified with column chromatography on silica gel using 20% EtOAc in hexane as eluent to give 1-benzyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde (0.406 g, 70%) as a white-yellow solid; mp 104-105°C (lit.⁶ 105-107°C); δ_{H} (300 MHz; CDCl₃; Me₄Si) 10.141 (1H, s, CHO), 7.95 (1H, t, *J* 3.0, benzimidazole-H), 7.44-7.15 (8H, m, benzimidazole-H and Ar-H), 5.85 (2H, s, -CH₂-); δ_{C} (75 MHz; CDCl₃) 184.9 (CHO), 145.9, 142.9, 136.6, 136.0, 128.9, 128.0, 127.1, 126.937, 124.2, 122.5, 111.4 and 48.0; HREI *m/z* 236.09 (*M*⁺, 100).

2-Phenyl- *N*-toluenesulfonylpyrrole 16

N-Toluenesulfonylpyrrole (0.884 g, 3.98 mmol) was treated according to the general method, with *i*-PrMgCl (9.95 mmol, 7.48 ml, 1.8 eq.) and (*i*-Pr)₂NH (56 μ L, 0.4 mmol, 10 mol %). Iodobenzene (0.89 ml, 7.96 mmol) and Pd(Ph₃P)₄ (0.231 g, 0.2 mmol) was added and the solution stirred at room temperature for 18 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH₄Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc. The combined organic phase were dried over MgSO₄ and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with dichloromethane / hexane (1:4) to yield the title compound as a brown solid (600 mg, 51%) mp. 122°C (Lit.⁷ 123-124°C) δ_{H} (300 MHz; CDCl₃; Me₄Si) 7.05-7.44 (10H, m, 9Ar-H and 1 pyrrole-H), 6.30 (1H, apparent t, *J* 3.3, pyrrole-H), 6.15 (1H, apparent dd, *J* 1.8 and 3.3, pyrrole-H) and 2.35 (3H, s, Me); δ_{C} (75 MHz; CDCl₃) 145.0, 136.4, 136.0, 131.7, 131.3, 129.7, 128.6, 127.7, 127.5, 124.5, 116.1, 112.4 and 21.9; HREI *m/z* 297.08 (*M*⁺, 100).

5-Methoxy-2-phenyl-1-phenylsulfonyl-1*H*-indole 18

5-Methoxy-1-phenylsulfonyl-1*H*-indole (2.42 mmol, 0.695 g) was treated according to the general method, with *i*-PrMgCl.LiCl (4.356 mmol, 3.27 ml, 1.8eq) and (*i*-Pr)₂NH (0.242 mmol, 34 μ L, 10 mol%) and left stirring at room temperature for 18 hrs. The reaction was treated with iodobenzene (0.49 ml, 4.356 mmol) and Pd(Ph₃P)₄ (231.16 mg, 0.2 mmol). After stirring at room temperature for 18 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH₄Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc (25 ml). The combined organic phase were dried over MgSO₄ and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with dichloromethane /hexane (1:4) to yield the title compound as a brown oil (0.527 g, 60%); δ_{H} (300 MHz; CDCl₃; Me₄Si) 8.19 (1H, d, *J* 9, Ar-H), 7.51-7.24 (10H, m, Ar-H and indole-H), 6.96 (1H, dd, *J* 2.4 and 9, indole-H), 6.88 (1H, d, *J* 2.4, indole-H), 6.48 (1H, s, indole-H) and 3.814 (3H, s, -OMe); δ_{C} (75 MHz; CDCl₃) 157.1, 143.0, 137.2, 133.4, 132.8, 132.3, 131.7, 130.2, 128.7, 128.5, 127.5, 126.7, 117.7, 113.9, 113.5, 103.2 and 55.6; HREI *m/z* 363.09 (Found 363.0924: C₂₁H₁₇O₃NS requires 363.0929).

2-(4-Bromo-2,5-dimethoxyphenyl)-1-phenylsulfonyl-1*H*-indole 19

1-Phenylsulfonyl-1*H*-indole (2.42 mmol, 0.622 g) was treated according to the general method with *i*-PrMgCl.LiCl (4.356 mmol, 3.27 ml, 1.8eq) and (*i*-Pr)₂NH (28 μ L, 0.2 mmol, 5 mol %). After standing at room temperature for 18 hours, the reaction was treated with 1,4-

dibromo-2,5-dimethoxybenzene (4.356 mmol, 1.280g) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (231.16 mg, 0.2 mmol). After stirring at room temperature for 18 hours, the reaction was partitioned between EtOAc (50 ml) and sat. aq. NH_4Cl (50 ml), the organic phase separated, the aqueous phase washed further with EtOAc. The combined organic phase were dried over MgSO_4 and the solvent removed under reduced pressure to give a brown oil which was further purified by column chromatography on silica gel, eluting with EtOAc / hexane (1:5) to yield the title compound as a brown solid (0.706 g, 62%) mp. 181-183°C; δ_{H} (300 MHz; CDCl_3 ; Me_4Si) 8.24 (1H, d, J 8.4, Ar-H), 7.51 -7.25 (8H, m, Ar-H and indole-H), 7.13 (1H, s, Ar-H), 6.78 (1H, s, Ar-H), 6.58 (1H, s, indole-H), 3.82 (3H, s, -OMe) and 3.68 (3H, s, -OMe); δ_{C} (75 MHz; CDCl_3) 153.1, 149.6, 139.0, 137.9, 137.0, 133.8, 130.4, 129.0, 127.1, 125.2, 124.3, 121.5, 121.3, 116.7, 116.5, 116.1, 113.5, 113.3, 57.4 and 56.5 ; HREI m/z 471.01 (Found 471.0151: $\text{C}_{22}\text{H}_{18}\text{O}_4\text{NBrS}$ requires 471.0139).

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